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NOVEL NUCLEIC ACIDS AND POLYPEPTIDES

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1. CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. Application Serial No. 09/552,317, filed April 25, 2000, which in turn is a continuation-in-part application of U.S. Application Serial No. 09/488,725, filed January 21, 2000, both of which are incorporated herein by reference in their entirety.

2. BACKGROUND OF THE INVENTION

2.1 TECHNICAL FIELD

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with uses for these polynucleotides and proteins, for example in therapeutic, diagnostic and research methods.

2.2 BACKGROUND

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs, chemokines, and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization-based cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity, for example, by virtue of their secreted nature in the

case of leader sequence cloning, by virtue of their cell or tissue source in the case of PCR-based techniques, or by virtue of structural similarity to other genes of known biological activity.

Identified polynucleotide and polypeptide sequences have numerous applications in, for example, diagnostics, forensics, gene mapping; identification of mutations responsible for genetic disorders or other traits, to assess biodiversity, and to produce many other types of data and products dependent on DNA and amino acid sequences.

3. SUMMARY OF THE INVENTION

The compositions of the present invention include novel isolated polypeptides, novel isolated polynucleotides encoding such polypeptides, including recombinant DNA molecules, cloned genes or degenerate variants thereof, especially naturally occurring variants such as allelic variants, antisense polynucleotide molecules, and antibodies that specifically recognize one or more epitopes present on such polypeptides, as well as hybridomas producing such antibodies.

The compositions of the present invention additionally include vectors, including expression vectors, containing the polynucleotides of the invention, cells genetically engineered to contain such polynucleotides and cells genetically engineered to express such polynucleotides.

The present invention relates to a collection or library of at least one novel nucleic acid sequence assembled from expressed sequence tags (ESTs) isolated mainly by sequencing by hybridization (SBH), and in some cases, sequences obtained from one or more public databases. The invention relates also to the proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins. These nucleic acid sequences are designated as SEQ ID NO: 1 - 1104 and are provided in the Sequence Listing. In the nucleic acids provided in the Sequence Listing, A is adenosine; C is cytosine; G is guanosine; T is thymine; and N is any of the four bases. In the amino acids provided in the Sequence Listing, * corresponds to the stop codon.

The nucleic acid sequences of the present invention also include, nucleic acid sequences that hybridize to the complement of SEQ ID NO: 1 – 1104 under stringent hybridization conditions; nucleic acid sequences which are allelic variants or species homologues of any of the nucleic acid sequences recited above, or nucleic acid sequences that encode a peptide comprising a specific domain or truncation of the peptides encoded by SEQ ID NO: 1 – 1104. A polynucleotide comprising a nucleotide sequence having at least 90% identity to an identifying sequence of SEQ ID NO: 1 – 1104 or a degenerate variant or fragment thereof. The identifying sequence can be 100 base pairs in length.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NO: 1 – 1104. The sequence information can be a segment of any one of SEQ ID NO: 1 – 1104 that uniquely identifies or represents the sequence information of SEQ ID NO: 1 – 1104.

A collection as used in this application can be a collection of only one polynucleotide. The collection of sequence information or identifying information of each sequence can be provided on a nucleic acid array. In one embodiment, segments of sequence information is provided on a nucleic acid array to detect the polynucleotide that contains the segment. The array can be designed to detect full-match or mismatch to the polynucleotide that contains the segment. The collection can also be provided in a computer-readable format.

This invention also includes the reverse or direct complement of any of the nucleic acid sequences recited above; cloning or expression vectors containing the nucleic acid sequences; and host cells or organisms transformed with these expression vectors. Nucleic acid sequences (or their reverse or direct complements) according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology, such as use as hybridization probes, use as primers for PCR, use in an array, use in computer-readable media, use in sequencing full-length genes, use for chromosome and gene mapping, use in the recombinant production of protein, and use in the generation of anti-sense DNA or RNA, their chemical analogs and the like.

In a preferred embodiment, the nucleic acid sequences of SEQ ID NO: 1-1104 or novel segments or parts of the nucleic acids of the invention are used as primers in

expression assays that are well known in the art. In a particularly preferred embodiment, the nucleic acid sequences of SEQ ID NO: 1-1104 or novel segments or parts of the nucleic acids provided herein are used in diagnostics for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

The isolated polynucleotides of the invention include, but are not limited to, a polynucleotide comprising any one of the nucleotide sequences set forth in the SEQ ID NO: 1-1104; a polynucleotide comprising any of the full length protein coding sequences of the SEQ ID NO: 1-1104; and a polynucleotide comprising any of the nucleotide sequences of the mature protein coding sequences of the SEQ ID NO: 1-1104. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent hybridization conditions to (a) the complement of any one of the nucleotide sequences set forth in the SEQ ID NO: 1-1104; (b) a nucleotide sequence encoding any one of the amino acid sequences set forth in the Sequence Listing; (c) a polynucleotide which is an allelic variant of any polynucleotides recited above; (d) a polynucleotide which encodes a species homolog (e.g. orthologs) of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of any of the polypeptides comprising an amino acid sequence set forth in the Sequence Listing.

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising any of the amino acid sequences set forth in the Sequence Listing; or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides with biological activity that are encoded by (a) any of the polynucleotides having a nucleotide sequence set forth in the SEQ ID NO: 1-1104; or (b) polynucleotides that hybridize to the complement of the polynucleotides of (a) under stringent hybridization conditions. Biologically or immunologically active variants of any of the polypeptide sequences in the Sequence Listing, and "substantial equivalents" thereof (e.g., with at least about 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% amino acid sequence identity) that preferably retain biological activity are also contemplated. The polypeptides of the invention may be wholly or partially chemically synthesized but are

preferably produced by recombinant means using the genetically engineered cells (e.g. host cells) of the invention.

The invention also provides compositions comprising a polypeptide of the invention. Polypeptide compositions of the invention may further comprise an acceptable carrier, such as a hydrophilic, e.g., pharmaceutically acceptable, carrier.

The invention also provides host cells transformed or transfected with a polynucleotide of the invention.

The invention also relates to methods for producing a polypeptide of the invention comprising growing a culture of the host cells of the invention in a suitable culture medium under conditions permitting expression of the desired polypeptide, and purifying the polypeptide from the culture or from the host cells. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Polynucleotides according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology. These techniques include use as hybridization probes, use as oligomers, or primers, for PCR, use for chromosome and gene mapping, use in the recombinant production of protein, and use in generation of anti-sense DNA or RNA, their chemical analogs and the like. For example, when the expression of an mRNA is largely restricted to a particular cell or tissue type, polynucleotides of the invention can be used as hybridization probes to detect the presence of the particular cell or tissue mRNA in a sample using, *e.g., in situ* hybridization.

In other exemplary embodiments, the polynucleotides are used in diagnostics as expressed sequence tags for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

The polypeptides according to the invention can be used in a variety of conventional procedures and methods that are currently applied to other proteins. For example, a polypeptide of the invention can be used to generate an antibody that specifically binds the polypeptide. Such antibodies, particularly monoclonal antibodies,

are useful for detecting or quantitating the polypeptide in tissue. The polypeptides of the invention can also be used as molecular weight markers, and as a food supplement.

Methods are also provided for preventing, treating, or ameliorating a medical condition which comprises the step of administering to a mammalian subject a therapeutically effective amount of a composition comprising a polypeptide of the present invention and a pharmaceutically acceptable carrier.

In particular, the polypeptides and polynucleotides of the invention can be utilized, for example, in methods for the prevention and/or treatment of disorders involving aberrant protein expression or biological activity.

The present invention further relates to methods for detecting the presence of the polynucleotides or polypeptides of the invention in a sample. Such methods can, for example, be utilized as part of prognostic and diagnostic evaluation of disorders as recited herein and for the identification of subjects exhibiting a predisposition to such conditions. The invention provides a method for detecting the polynucleotides of the invention in a sample, comprising contacting the sample with a compound that binds to and forms a complex with the polynucleotide of interest for a period sufficient to form the complex and under conditions sufficient to form a complex and detecting the complex such that if a complex is detected, the polynucleotide of interest is detected. The invention also provides a method for detecting the polypeptides of the invention in a sample comprising contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex and detecting the formation of the complex such that if a complex is formed, the polypeptide is detected.

The invention also provides kits comprising polynucleotide probes and/or monoclonal antibodies, and optionally quantitative standards, for carrying out methods of the invention. Furthermore, the invention provides methods for evaluating the efficacy of drugs, and monitoring the progress of patients, involved in clinical trials for the treatment of disorders as recited above.

The invention also provides methods for the identification of compounds that modulate (i.e., increase or decrease) the expression or activity of the polynucleotides

and/or polypeptides of the invention. Such methods can be utilized, for example, for the identification of compounds that can ameliorate symptoms of disorders as recited herein. Such methods can include, but are not limited to, assays for identifying compounds and other substances that interact with (*e.g.*, bind to) the polypeptides of the invention. The invention provides a method for identifying a compound that binds to the polypeptides of the invention comprising contacting the compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and detecting the complex by detecting the reporter gene sequence expression such that if expression of the reporter gene is detected the compound the binds to a polypeptide of the invention is identified.

The methods of the invention also provides methods for treatment which involve the administration of the polynucleotides or polypeptides of the invention to individuals exhibiting symptoms or tendencies. In addition, the invention encompasses methods for treating diseases or disorders as recited herein comprising administering compounds and other substances that modulate the overall activity of the target gene products. Compounds and other substances can effect such modulation either on the level of target gene/protein expression or target protein activity.

The polypeptides of the present invention and the polynucleotides encoding them are also useful for the same functions known to one of skill in the art as the polypeptides and polynucleotides to which they have the closest homology (set forth in Table 1). If no homology is set forth for a sequence, then the polypeptides and polynucleotides of the present invention are useful for a variety of applications, as described herein, including use in arrays for detection.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 DEFINITIONS

It must be noted that as used herein and in the appended claims, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

The term "active" refers to those forms of the polypeptide which retain the biologic and/or immunologic activities of any naturally occurring polypeptide. According to the invention, the terms "biologically active" or "biological activity" refer to a protein or peptide having structural, regulatory or biochemical functions of a naturally occurring molecule. Likewise "immunologically active" or "immunological activity" refers to the capability of the natural, recombinant or synthetic polypeptide to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The term "activated cells" as used in this application are those cells which are engaged in extracellular or intracellular membrane trafficking, including the export of secretory or enzymatic molecules as part of a normal or disease process.

The terms "complementary" or "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence 5'-AGT-3' binds to the complementary sequence 3'-TCA-5'. Complementarity between two single-stranded molecules may be "partial" such that only some of the nucleic acids bind or it may be "complete" such that total complementarity exists between the single stranded molecules. The degree of complementarity between the nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands.

The term "embryonic stem cells (ES)" refers to a cell that can give rise to many differentiated cell types in an embryo or an adult, including the germ cells. The term "germ line stem cells (GSCs)" refers to stem cells derived from primordial stem cells that provide a steady and continuous source of germ cells for the production of gametes. The term "primordial germ cells (PGCs)" refers to a small population of cells set aside from other cell lineages particularly from the yolk sac, mesenteries, or gonadal ridges during embryogenesis that have the potential to differentiate into germ cells and other cells. PGCs are the source from which GSCs and ES cells are derived

The PGCs, the GSCs and the ES cells are capable of self-renewal. Thus these cells not only populate the germ line and give rise to a plurality of terminally differentiated cells that comprise the adult specialized organs, but are able to regenerate themselves.

The term "expression modulating fragment," EMF, means a series of nucleotides which modulates the expression of an operably linked ORF or another EMF.

As used herein, a sequence is said to "modulate the expression of an operably linked sequence" when the expression of the sequence is altered by the presence of the EMF. EMFs include, but are not limited to, promoters, and promoter modulating sequences (inducible elements). One class of EMFs are nucleic acid fragments which induce the expression of an operably linked ORF in response to a specific regulatory factor or physiological event.

The terms "nucleotide sequence" or "nucleic acid" or "polynucleotide" or "oligonculeotide" are used interchangeably and refer to a heteropolymer of nucleotides or the sequence of these nucleotides. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA) or to any DNA-like or RNA-like material. Generally, nucleic acid segments provided by this invention may be assembled from fragments of the genome and short oligonucleotide linkers, or from a series of oligonucleotides, or from individual nucleotides, to provide a synthetic nucleic acid which is capable of being expressed in a recombinant transcriptional unit comprising regulatory elements derived from a microbial or viral operon, or a eukaryotic gene.

The terms "oligonucleotide fragment" or a "polynucleotide fragment", "portion," or "segment" or "probe" or "primer" are used interchangeable and refer to a sequence of nucleotide residues which are at least about 5 nucleotides, more preferably at least about 7 nucleotides, more preferably at least about 9 nucleotides, more preferably at least about 11 nucleotides and most preferably at least about 17 nucleotides. The fragment is preferably less than about 500 nucleotides, preferably less than about 200 nucleotides, more preferably less than about 100 nucleotides, more

preferably less than about 50 nucleotides and most preferably less than 30 nucleotides. Preferably the probe is from about 6 nucleotides to about 200 nucleotides, preferably from about 15 to about 50 nucleotides, more preferably from about 17 to 30 nucleotides and most preferably from about 20 to 25 nucleotides. Preferably the fragments can be used in polymerase chain reaction (PCR), various hybridization procedures or microarray procedures to identify or amplify identical or related parts of mRNA or DNA molecules. A fragment or segment may uniquely identify each polynucleotide sequence of the present invention. Preferably the fragment comprises a sequence substantially similar to any one of SEQ ID NOs:1-1104.

Probes may, for example, be used to determine whether specific mRNA molecules are present in a cell or tissue or to isolate similar nucleic acid sequences from chromosomal DNA as described by Walsh et al. (Walsh, P.S. et al., 1992, PCR Methods Appl 1:241-250). They may be labeled by nick translation, Klenow fill-in reaction, PCR, or other methods well known in the art. Probes of the present invention, their preparation and/or labeling are elaborated in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY; or Ausubel, F.M. et al., 1989, Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, both of which are incorporated herein by reference in their entirety.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NOs: 1-1104. The sequence information can be a segment of any one of SEQ ID NOs: 1-1104 that uniquely identifies or represents the sequence information of that sequence of SEQ ID NO: 1-1104. One such segment can be a twenty-mer nucleic acid sequence because the probability that a twenty-mer is fully matched in the human genome is 1 in 300. In the human genome, there are three billion base pairs in one set of chromosomes. Because 4^{20} possible twenty-mers exist, there are 300 times more twenty-mers than there are base pairs in a set of human chromosome. Using the same analysis, the probability for a seventeen-mer to be fully matched in the human genome is approximately 1 in 5. When these segments are used in arrays for expression studies, fifteen-mer segments

can be used. The probability that the fifteen-mer is fully matched in the expressed sequences is also approximately one in five because expressed sequences comprise less than approximately 5% of the entire genome sequence.

Similarly, when using sequence information for detecting a single mismatch, a segment can be a twenty-five mer. The probability that the twenty-five mer would appear in a human genome with a single mismatch is calculated by multiplying the probability for a full match ($1 \div 4^{25}$) times the increased probability for mismatch at each nucleotide position (3 x 25). The probability that an eighteen mer with a single mismatch can be detected in an array for expression studies is approximately one in five. The probability that a twenty-mer with a single mismatch can be detected in a human genome is approximately one in five.

The term "open reading frame," ORF, means a series of nucleotide triplets coding for amino acids without any termination codons and is a sequence translatable into protein.

The terms "operably linked" or "operably associated" refer to functionally related nucleic acid sequences. For example, a promoter is operably associated or operably linked with a coding sequence if the promoter controls the transcription of the coding sequence. While operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements e.g. repressor genes are not contiguously linked to the coding sequence but still control transcription/translation of the coding sequence.

The term "pluripotent" refers to the capability of a cell to differentiate into a number of differentiated cell types that are present in an adult organism. A pluripotent cell is restricted in its differentiation capability in comparison to a totipotent cell.

The terms "polypeptide" or "peptide" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide or protein sequence or fragment thereof and to naturally occurring or synthetic molecules. A polypeptide "fragment," "portion," or "segment" is a stretch of amino acid residues of at least about 5 amino acids, preferably at least about 7 amino acids, more preferably at least about 9 amino acids and most preferably at least about 17 or more amino acids. The peptide preferably is not greater

than about 200 amino acids, more preferably less than 150 amino acids and most preferably less than 100 amino acids. Preferably the peptide is from about 5 to about 200 amino acids. To be active, any polypeptide must have sufficient length to display biological and/or immunological activity.

The term "naturally occurring polypeptide" refers to polypeptides produced by cells that have not been genetically engineered and specifically contemplates various polypeptides arising from post-translational modifications of the polypeptide including, but not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation.

The term "translated protein coding portion" means a sequence which encodes for the full length protein which may include any leader sequence or any processing sequence.

The term "mature protein coding sequence" means a sequence which encodes a peptide or protein without a signal or leader sequence. The peptide may have been produced by processing in the cell which removes any leader/signal sequence. The peptide may be produced synthetically or the protein may have been produced using a polynucleotide only encoding for the mature protein coding sequence.

The term "derivative" refers to polypeptides chemically modified by such techniques as ubiquitination, labeling (e.g., with radionuclides or various enzymes), covalent polymer attachment such as pegylation (derivatization with polyethylene glycol) and insertion or substitution by chemical synthesis of amino acids such as ornithine, which do not normally occur in human proteins.

The term "variant"(or "analog") refers to any polypeptide differing from naturally occurring polypeptides by amino acid insertions, deletions, and substitutions, created using, *e g.*, recombinant DNA techniques. Guidance in determining which amino acid residues may be replaced, added or deleted without abolishing activities of interest, may be found by comparing the sequence of the particular polypeptide with that of homologous peptides and minimizing the number of amino acid sequence changes made in regions of high homology (conserved regions) or by replacing amino acids with consensus sequence.

Alternatively, recombinant variants encoding these same or similar polypeptides may be synthesized or selected by making use of the "redundancy" in the genetic code. Various codon substitutions, such as the silent changes which produce various restriction sites, may be introduced to optimize cloning into a plasmid or viral vector or expression in a particular prokaryotic or eukaryotic system. Mutations in the polynucleotide sequence may be reflected in the polypeptide or domains of other peptides added to the polypeptide to modify the properties of any part of the polypeptide, to change characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate.

Preferably, amino acid "substitutions" are the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, *i.e.*, conservative amino acid replacements. "Conservative" amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid. "Insertions" or "deletions" are preferably in the range of about 1 to 20 amino acids, more preferably 1 to 10 amino acids. The variation allowed may be experimentally determined by systematically making insertions, deletions, or substitutions of amino acids in a polypeptide molecule using recombinant DNA techniques and assaying the resulting recombinant variants for activity.

Alternatively, where alteration of function is desired, insertions, deletions or non-conservative alterations can be engineered to produce altered polypeptides. Such alterations can, for example, alter one or more of the biological functions or biochemical characteristics of the polypeptides of the invention. For example, such alterations may change polypeptide characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate. Further, such alterations can be

selected so as to generate polypeptides that are better suited for expression, scale up and the like in the host cells chosen for expression. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges.

The terms "purified" or "substantially purified" as used herein denotes that the indicated nucleic acid or polypeptide is present in the substantial absence of other biological macromolecules, *e.g.*, polynucleotides, proteins, and the like. In one embodiment, the polynucleotide or polypeptide is purified such that it constitutes at least 95% by weight, more preferably at least 99% by weight, of the indicated biological macromolecules present (but water, buffers, and other small molecules, especially molecules having a molecular weight of less than 1000 daltons, can be present).

The term "isolated" as used herein refers to a nucleic acid or polypeptide separated from at least one other component (e.g., nucleic acid or polypeptide) present with the nucleic acid or polypeptide in its natural source. In one embodiment, the nucleic acid or polypeptide is found in the presence of (if anything) only a solvent, buffer, ion, or other component normally present in a solution of the same. The terms "isolated" and "purified" do not encompass nucleic acids or polypeptides present in their natural source.

The term "recombinant," when used herein to refer to a polypeptide or protein, means that a polypeptide or protein is derived from recombinant (*e.g.*, microbial, insect, or mammalian) expression systems. "Microbial" refers to recombinant polypeptides or proteins made in bacterial or fungal (e.g., yeast) expression systems. As a product, "recombinant microbial" defines a polypeptide or protein essentially free of native endogenous substances and unaccompanied by associated native glycosylation. Polypeptides or proteins expressed in most bacterial cultures, *e.g., E. coli*, will be free of glycosylation modifications; polypeptides or proteins expressed in yeast will have a glycosylation pattern in general different from those expressed in mammalian cells.

The term "recombinant expression vehicle or vector" refers to a plasmid or phage or virus or vector, for expressing a polypeptide from a DNA (RNA) sequence.

An expression vehicle can comprise a transcriptional unit comprising an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers, (2) a structural or coding sequence which is transcribed into mRNA and translated into protein, and (3) appropriate transcription initiation and termination sequences. Structural units intended for use in yeast or eukaryotic expression systems preferably include a leader sequence enabling extracellular secretion of translated protein by a host cell. Alternatively, where recombinant protein is expressed without a leader or transport sequence, it may include an amino terminal methionine residue. This residue may or may not be subsequently cleaved from the expressed recombinant protein to provide a final product.

The term "recombinant expression system" means host cells which have stably integrated a recombinant transcriptional unit into chromosomal DNA or carry the recombinant transcriptional unit extrachromosomally. Recombinant expression systems as defined herein will express heterologous polypeptides or proteins upon induction of the regulatory elements linked to the DNA segment or synthetic gene to be expressed. This term also means host cells which have stably integrated a recombinant genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers. Recombinant expression systems as defined herein will express polypeptides or proteins endogenous to the cell upon induction of the regulatory elements linked to the endogenous DNA segment or gene to be expressed. The cells can be prokaryotic or eukaryotic.

The term "secreted" includes a protein that is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence when it is expressed in a suitable host cell. "Secreted" proteins include without limitation proteins secreted wholly (*e.g.*, soluble proteins) or partially (*e.g.*, receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins that are transported across the membrane of the endoplasmic reticulum. "Secreted" proteins are also intended to include proteins containing non-typical signal sequences (e.g. Interleukin-1 Beta, see Krasney, P.A. and Young, P.R. (1992) Cytokine 4(2):134 -143) and factors released from damaged cells (e.g.

Interleukin-1 Receptor Antagonist, see Arend, W.P. et. al. (1998) Annu. Rev. Immunol. 16:27-55)

Where desired, an expression vector may be designed to contain a "signal or leader sequence" which will direct the polypeptide through the membrane of a cell. Such a sequence may be naturally present on the polypeptides of the present invention or provided from heterologous protein sources by recombinant DNA techniques.

The term "stringent" is used to refer to conditions that are commonly understood in the art as stringent. Stringent conditions can include highly stringent conditions (i.e., hybridization to filter-bound DNA in 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1X SSC/0.1% SDS at 68°C), and moderately stringent conditions (i.e., washing in 0.2X SSC/0.1% SDS at 42°C). Other exemplary hybridization conditions are described herein in the examples.

In instances of hybridization of deoxyoligonucleotides, additional exemplary stringent hybridization conditions include washing in 6X SSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligonucleotides), 48°C (for 17-base oligos), 55°C (for 20-base oligonucleotides), and 60°C (for 23-base oligonucleotides).

As used herein, "substantially equivalent" can refer both to nucleotide and amino acid sequences, for example a mutant sequence, that varies from a reference sequence by one or more substitutions, deletions, or additions, the net effect of which does not result in an adverse functional dissimilarity between the reference and subject sequences. Typically, such a substantially equivalent sequence varies from one of those listed herein by no more than about 35% (*i.e.*, the number of individual residue substitutions, additions, and/or deletions in a substantially equivalent sequence, as compared to the corresponding reference sequence, divided by the total number of residues in the substantially equivalent sequence is about 0.35 or less). Such a sequence is said to have 65% sequence identity to the listed sequence. In one embodiment, a substantially equivalent, *e.g.*, mutant, sequence of the invention varies from a listed sequence by no more than 30% (70% sequence identity); in a variation of this embodiment, by no more than 25% (75% sequence identity); and in a further variation of this embodiment, by no more than 20% (80% sequence identity) and in a

further variation of this embodiment, by no more than 10% (90% sequence identity) and in a further variation of this embodiment, by no more that 5% (95% sequence identity). Substantially equivalent, *e.g.*, mutant, amino acid sequences according to the invention preferably have at least 80% sequence identity with a listed amino acid sequence, more preferably at least 90% sequence identity. Substantially equivalent nucleotide sequences of the invention can have lower percent sequence identities, taking into account, for example, the redundancy or degeneracy of the genetic code. Preferably, nucleotide sequence has at least about 65% identity, more preferably at least about 75% identity, and most preferably at least about 95% identity. For the purposes of the present invention, sequences having substantially equivalent biological activity and substantially equivalent expression characteristics are considered substantially equivalent. For the purposes of determining equivalence, truncation of the mature sequence (*e.g.*, via a mutation which creates a spurious stop codon) should be disregarded. Sequence identity may be determined, e.g., using the Jotun Hein method (Hein, J. (1990) Methods Enzymol. 183:626-645). Identity between sequences can also be determined by other methods known in the art, e.g. by varying hybridization conditions.

The term "totipotent" refers to the capability of a cell to differentiate into all of the cell types of an adult organism.

The term "transformation" means introducing DNA into a suitable host cell so that the DNA is replicable, either as an extrachromosomal element, or by chromosomal integration. The term "transfection" refers to the taking up of an expression vector by a suitable host cell, whether or not any coding sequences are in fact expressed. The term "infection" refers to the introduction of nucleic acids into a suitable host cell by use of a virus or viral vector.

As used herein, an "uptake modulating fragment," UMF, means a series of nucleotides which mediate the uptake of a linked DNA fragment into a cell. UMFs can be readily identified using known UMFs as a target sequence or target motif with the computer-based systems described below. The presence and activity of a UMF can be confirmed by attaching the suspected UMF to a marker sequence. The resulting nucleic

acid molecule is then incubated with an appropriate host under appropriate conditions and the uptake of the marker sequence is determined. As described above, a UMF will increase the frequency of uptake of a linked marker sequence.

Each of the above terms is meant to encompass all that is described for each, unless the context dictates otherwise.

4.2 NUCLEIC ACIDS OF THE INVENTION

Nucleotide sequences of the invention are set forth in the Sequence Listing.

The isolated polynucleotides of the invention include a polynucleotide comprising the nucleotide sequences of the SEQ ID NO: 1 – 1104; a polynucleotide encoding any one of the peptide sequences of SEQ ID NO:1 – 1104; and a polynucleotide comprising the nucleotide sequence encoding the mature protein coding sequence of the polynucleotides of any one of SEQ ID NO: 1 - 1104. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent conditions to (a) the complement of any of the nucleotides sequences of the SEQ ID NO: 1 – 1104; (b) nucleotide sequences encoding any one of the amino acid sequences set forth in the Sequence Listing; (c) a polynucleotide which is an allelic variant of any polynucleotide recited above; (d) a polynucleotide which encodes a species homolog of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of the polypeptides of SEQ ID NO: 1- 1104. Domains of interest may depend on the nature of the encoded polypeptide; e.g., domains in receptor-like polypeptides include ligand-binding, extracellular, transmembrane, or cytoplasmic domains, or combinations thereof; domains in immunoglobulin-like proteins include the variable immunoglobulin-like domains; domains in enzyme-like polypeptides include catalytic and substrate binding domains; and domains in ligand polypeptides include receptor-binding domains.

The polynucleotides of the invention include naturally occurring or wholly or partially synthetic DNA, e.g., cDNA and genomic DNA, and RNA, e.g., mRNA. The

polynucleotides may include all of the coding region of the cDNA or may represent a portion of the coding region of the cDNA.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. Further 5' and 3' sequence can be obtained using methods known in the art. For example, full length cDNA or genomic DNA that corresponds to any of the polynucleotides of the SEQ ID NO: 1 – 1104 can be obtained by screening appropriate cDNA or genomic DNA libraries under suitable hybridization conditions using any of the polynucleotides of the SEQ ID NO: 1 - 1104 or a portion thereof as a probe. Alternatively, the polynucleotides of the SEQ ID NO: 1 - 1104 may be used as the basis for suitable primer(s) that allow identification and/or amplification of genes in appropriate genomic DNA or cDNA libraries.

The nucleic acid sequences of the invention can be assembled from ESTs and sequences (including cDNA and genomic sequences) obtained from one or more public databases, such as dbEST, gbpri, and UniGene. The EST sequences can provide identifying sequence information, representative fragment or segment information, or novel segment information for the full-length gene.

The polynucleotides of the invention also provide polynucleotides including nucleotide sequences that are substantially equivalent to the polynucleotides recited above. Polynucleotides according to the invention can have, *e.g.*, at least about 65%, at least about 70%, at least about 75%, at least about 80%, more typically at least about 90%, and even more typically at least about 95%, sequence identity to a polynucleotide recited above.

Included within the scope of the nucleic acid sequences of the invention are nucleic acid sequence fragments that hybridize under stringent conditions to any of the nucleotide sequences of the SEQ ID NO: 1 - 1104, or complements thereof, which fragment is greater than about 5 nucleotides, preferably 7 nucleotides, more preferably

greater than 9 nucleotides and most preferably greater than 17 nucleotides. Fragments of, e.g. 15, 17, or 20 nucleotides or more that are selective for (i.e. specifically hybridize to any one of the polynucleotides of the invention) are contemplated. Probes capable of specifically hybridizing to a polynucleotide can differentiate polynucleotide sequences of the invention from other polynucleotide sequences in the same family of genes or can differentiate human genes from genes of other species, and are preferably based on unique nucleotide sequences.

The sequences falling within the scope of the present invention are not limited to these specific sequences, but also include allelic and species variations thereof. Allelic and species variations can be routinely determined by comparing the sequence provided in SEQ ID NO: 1 - 1104, a representative fragment thereof, or a nucleotide sequence at least 90% identical, preferably 95% identical, to SEQ ID NOs: 1 - 1104 with a sequence from another isolate of the same species. Furthermore, to accommodate codon variability, the invention includes nucleic acid molecules coding for the same amino acid sequences as do the specific ORFs disclosed herein. In other words, in the coding region of an ORF, substitution of one codon for another codon that encodes the same amino acid is expressly contemplated.

The nearest neighbor result for the nucleic acids of the present invention, including SEQ ID NOs: 1 - 1104, can be obtained by searching a database using an algorithm or a program. Preferably, a BLAST which stands for Basic Local Alignment Search Tool is used to search for local sequence alignments (Altshul, S.F. J Mol. Evol. 36 290-300 (1993) and Altschul S.F. et al. J. Mol. Biol. 21:403-410 (1990)). Alternatively a FASTA version 3 search against Genpept, using Fastxy algorithm.

Species homologs (or orthologs) of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide

which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides.

The nucleic acid sequences of the invention are further directed to sequences which encode variants of the described nucleic acids. These amino acid sequence variants may be prepared by methods known in the art by introducing appropriate nucleotide changes into a native or variant polynucleotide. There are two variables in the construction of amino acid sequence variants: the location of the mutation and the nature of the mutation. Nucleic acids encoding the amino acid sequence variants are preferably constructed by mutating the polynucleotide to encode an amino acid sequence that does not occur in nature. These nucleic acid alterations can be made at sites that differ in the nucleic acids from different species (variable positions) or in highly conserved regions (constant regions). Sites at such locations will typically be modified in series, *e.g.*, by substituting first with conservative choices (*e.g.*, hydrophobic amino acid to a different hydrophobic amino acid) and then with more distant choices (*e.g.*, hydrophobic amino acid to a charged amino acid), and then deletions or insertions may be made at the target site. Amino acid sequence deletions generally range from about 1 to 30 residues, preferably about 1 to 10 residues, and are typically contiguous. Amino acid insertions include amino- and/or carboxyl-terminal fusions ranging in length from one to one hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Intrasequence insertions may range generally from about 1 to 10 amino residues, preferably from 1 to 5 residues. Examples of terminal insertions include the heterologous signal sequences necessary for secretion or for intracellular targeting in different host cells and sequences such as FLAG or poly-histidine sequences useful for purifying the expressed protein.

In a preferred method, polynucleotides encoding the novel amino acid sequences are changed via site-directed mutagenesis. This method uses oligonucleotide sequences to alter a polynucleotide to encode the desired amino acid variant, as well as sufficient adjacent nucleotides on both sides of the changed amino acid to form a stable duplex on either side of the site of being changed. In general, the techniques of site-directed

mutagenesis are well known to those of skill in the art and this technique is exemplified by publications such as, Edelman et al., *DNA* 2:183 (1983). A versatile and efficient method for producing site-specific changes in a polynucleotide sequence was published by Zoller and Smith, *Nucleic Acids Res.* 10:6487-6500 (1982). PCR may also be used to create amino acid sequence variants of the novel nucleic acids. When small amounts of template DNA are used as starting material, primer(s) that differs slightly in sequence from the corresponding region in the template DNA can generate the desired amino acid variant. PCR amplification results in a population of product DNA fragments that differ from the polynucleotide template encoding the polypeptide at the position specified by the primer. The product DNA fragments replace the corresponding region in the plasmid and this gives a polynucleotide encoding the desired amino acid variant.

A further technique for generating amino acid variants is the cassette mutagenesis technique described in Wells et al., *Gene* 34:315 (1985); and other mutagenesis techniques well known in the art, such as, for example, the techniques in Sambrook et al., supra, and *Current Protocols in Molecular Biology*, Ausubel et al. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be used in the practice of the invention for the cloning and expression of these novel nucleic acids. Such DNA sequences include those which are capable of hybridizing to the appropriate novel nucleic acid sequence under stringent conditions.

Polynucleotides encoding preferred polypeptide truncations of the invention can be used to generate polynucleotides encoding chimeric or fusion proteins comprising one or more domains of the invention and heterologous protein sequences.

The polynucleotides of the invention additionally include the complement of any of the polynucleotides recited above. The polynucleotide can be DNA (genomic, cDNA, amplified, or synthetic) or RNA. Methods and algorithms for obtaining such polynucleotides are well known to those of skill in the art and can include, for example, methods for determining hybridization conditions that can routinely isolate polynucleotides of the desired sequence identities.

In accordance with the invention, polynucleotide sequences comprising the mature protein coding sequences corresponding to any one of SEQ ID NO: 1-1104, or functional equivalents thereof, may be used to generate recombinant DNA molecules that direct the expression of that nucleic acid, or a functional equivalent thereof, in appropriate host cells. Also included are the cDNA inserts of any of the clones identified herein.

A polynucleotide according to the invention can be joined to any of a variety of other nucleotide sequences by well-established recombinant DNA techniques (see Sambrook J et al. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY). Useful nucleotide sequences for joining to polynucleotides include an assortment of vectors, e.g., plasmids, cosmids, lambda phage derivatives, phagemids, and the like, that are well known in the art. Accordingly, the invention also provides a vector including a polynucleotide of the invention and a host cell containing the polynucleotide. In general, the vector contains an origin of replication functional in at least one organism, convenient restriction endonuclease sites, and a selectable marker for the host cell. Vectors according to the invention include expression vectors, replication vectors, probe generation vectors, and sequencing vectors. A host cell according to the invention can be a prokaryotic or eukaryotic cell and can be a unicellular organism or part of a multicellular organism.

The present invention further provides recombinant constructs comprising a nucleic acid having any of the nucleotide sequences of the SEQ ID NOs: 1 - 1104 or a fragment thereof or any other polynucleotides of the invention. In one embodiment, the recombinant constructs of the present invention comprise a vector, such as a plasmid or viral vector, into which a nucleic acid having any of the nucleotide sequences of the SEQ ID NOs: 1 - 1104 or a fragment thereof is inserted, in a forward or reverse orientation. In the case of a vector comprising one of the ORFs of the present invention, the vector may further comprise regulatory sequences, including for example, a promoter, operably linked to the ORF. Large numbers of suitable vectors and promoters are known to those of skill in the art and are commercially available for generating the recombinant constructs of the present invention. The following vectors

are provided by way of example. Bacterial: pBs, phagescript, PsiX174, pBluescript SK, pBs KS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia). Eukaryotic: pWLneo, pSV2cat, pOG44, PXTI, pSG (Stratagene) pSVK3, pBPV, pMSG, pSVL (Pharmacia).

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman et al., *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters include lacI, lacZ, T3, T7, gpt, lambda PR, and trc. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art. Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, *e.g.*, the ampicillin resistance gene of *E. coli* and *S. cerevisiae* TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), a-factor, acid phosphatase, or heat shock proteins, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium. Optionally,

the heterologous sequence can encode a fusion protein including an amino terminal identification peptide imparting desired characteristics, *e.g.*, stabilization or simplified purification of expressed recombinant product. Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and to, if desirable, provide amplification within the host. Suitable prokaryotic hosts for transformation include *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium* and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*, although others may also be employed as a matter of choice.

As a representative but non-limiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM 1 (Promega Biotech, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed. Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is induced or derepressed by appropriate means (*e.g.*, temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

Polynucleotides of the invention can also be used to induce immune responses. For example, as described in Fan et al., *Nat. Biotech.* 17:870-872 (1999), incorporated herein by reference, nucleic acid sequences encoding a polypeptide may be used to generate antibodies against the encoded polypeptide following topical administration of naked plasmid DNA or following injection, and preferably intramuscular injection of the DNA. The nucleic acid sequences are preferably inserted in a recombinant expression vector and may be in the form of naked DNA.

4.3 HOSTS

The present invention further provides host cells genetically engineered to contain the polynucleotides of the invention. For example, such host cells may contain nucleic acids of the invention introduced into the host cell using known transformation, transfection or infection methods. The present invention still further provides host cells genetically engineered to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell which drives expression of the polynucleotides in the cell.

Knowledge of nucleic acid sequences allows for modification of cells to permit, or increase, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express the polypeptide at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the encoding sequences. See, for example, PCT International Publication No. WO94/12650, PCT International Publication No. WO92/20808, and PCT International Publication No. WO91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., ada, dhfr, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the desired protein coding sequences in the cells.

The host cell can be a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the recombinant construct into the host cell can be effected by calcium phosphate transfection, DEAE, dextran mediated transfection, or electroporation (Davis, L. et al., *Basic Methods in Molecular Biology* (1986)). The host cells containing one of the polynucleotides of the invention, can be used in conventional manners to produce the gene product encoded by the isolated

fragment (in the case of an ORF) or can be used to produce a heterologous protein under the control of the EMF.

Any host/vector system can be used to express one or more of the ORFs of the present invention. These include, but are not limited to, eukaryotic hosts such as HeLa cells, Cv-1 cell, COS cells, 293 cells, and Sf9 cells, as well as prokaryotic host such as *E. coli* and *B. subtilis*. The most preferred cells are those which do not normally express the particular polypeptide or protein or which expresses the polypeptide or protein at low natural level. Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook, et al., in Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, New York (1989), the disclosure of which is hereby incorporated by reference.

Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts, described by Gluzman, Cell 23:175 (1981). Other cell lines capable of expressing a compatible vector are, for example, the C127, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5′ flanking nontranscribed sequences. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early promoter, enhancer, splice, and polyadenylation sites may be used to provide the required nontranscribed genetic elements. Recombinant polypeptides and proteins produced in bacterial culture are usually isolated by initial extraction from cell pellets, followed by one or more

salting-out, aqueous ion exchange or size exclusion chromatography steps. Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps. Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or insects or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequence include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or

modifying transport or secretion properties of the protein, or other sequences which alter or improve the function or stability of protein or RNA molecules.

The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, *e.g.*, inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally occurring elements. Here, the naturally occurring sequences are deleted and new sequences are added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the host cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

The gene targeting or gene activation techniques which can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

4.4 POLYPEPTIDES OF THE INVENTION

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising: the amino acid sequences set forth as any one of SEQ ID NO: 1-1104 or an amino acid sequence encoded by any one of the nucleotide sequences SEQ ID NOs: 1 - 1104 or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides preferably with biological or immunological activity that are encoded by: (a) a polynucleotide having any one of the nucleotide sequences set forth in the SEQ ID NOs: 1 - 1104 or (b) polynucleotides encoding any one of the amino acid sequences set forth as SEQ ID NO: 1-1104 or (c) polynucleotides that hybridize to the complement of the polynucleotides of either (a) or (b) under stringent hybridization conditions. The invention also provides biologically active or immunologically active variants of any of the amino acid sequences set forth as SEQ ID NO: 1-1104 or the corresponding full length or mature protein; and "substantial equivalents" thereof (e.g., with at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, typically at least about 95%, more typically at least about 98%, or most typically at least about 99% amino acid identity) that retain biological activity. Polypeptides encoded by allelic variants may have a similar, increased, or decreased activity compared to polypeptides comprising SEQ ID NO: 1-1104.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H. U. Saragovi, et al., Bio/Technology 10, 773-778 (1992) and in R. S. McDowell, et al., J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites.

The present invention also provides both full-length and mature forms (for example, without a signal sequence or precursor sequence) of the disclosed proteins. The protein coding sequence is identified in the sequence listing by translation of the disclosed nucleotide sequences. The mature form of such protein may be obtained by

expression of a full-length polynucleotide in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein is also determinable from the amino acid sequence of the full-length form. Where proteins of the present invention are membrane bound, soluble forms of the proteins are also provided. In such forms, part or all of the regions causing the proteins to be membrane bound are deleted so that the proteins are fully secreted from the cell in which it is expressed.

Protein compositions of the present invention may further comprise an acceptable carrier, such as a hydrophilic, *e.g.*, pharmaceutically acceptable, carrier.

The present invention further provides isolated polypeptides encoded by the nucleic acid fragments of the present invention or by degenerate variants of the nucleic acid fragments of the present invention. By "degenerate variant" is intended nucleotide fragments which differ from a nucleic acid fragment of the present invention (*e.g.*, an ORF) by nucleotide sequence but, due to the degeneracy of the genetic code, encode an identical polypeptide sequence. Preferred nucleic acid fragments of the present invention are the ORFs that encode proteins.

A variety of methodologies known in the art can be utilized to obtain any one of the isolated polypeptides or proteins of the present invention. At the simplest level, the amino acid sequence can be synthesized using commercially available peptide synthesizers. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. This technique is particularly useful in producing small peptides and fragments of larger polypeptides. Fragments are useful, for example, in generating antibodies against the native polypeptide. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The polypeptides and proteins of the present invention can alternatively be purified from cells which have been altered to express the desired polypeptide or protein. As used herein, a cell is said to be altered to express a desired polypeptide or

protein when the cell, through genetic manipulation, is made to produce a polypeptide or protein which it normally does not produce or which the cell normally produces at a lower level. One skilled in the art can readily adapt procedures for introducing and expressing either recombinant or synthetic sequences into eukaryotic or prokaryotic cells in order to generate a cell which produces one of the polypeptides or proteins of the present invention.

The invention also relates to methods for producing a polypeptide comprising growing a culture of host cells of the invention in a suitable culture medium, and purifying the protein from the cells or the culture in which the cells are grown. For example, the methods of the invention include a process for producing a polypeptide in which a host cell containing a suitable expression vector that includes a polynucleotide of the invention is cultured under conditions that allow expression of the encoded polypeptide. The polypeptide can be recovered from the culture, conveniently from the culture medium, or from a lysate prepared from the host cells and further purified. Preferred embodiments include those in which the protein produced by such process is a full length or mature form of the protein.

In an alternative method, the polypeptide or protein is purified from bacterial cells which naturally produce the polypeptide or protein. One skilled in the art can readily follow known methods for isolating polypeptides and proteins in order to obtain one of the isolated polypeptides or proteins of the present invention. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography, and immuno-affinity chromatography. See, *e.g.*, Scopes, *Protein Purification: Principles and Practice*, Springer-Verlag (1994); Sambrook, et al., in Molecular Cloning: *A Laboratory Manual*; Ausubel et al., *Current Protocols in Molecular Biology*. Polypeptide fragments that retain biological/immunological activity include fragments comprising greater than about 100 amino acids, or greater than about 200 amino acids, and fragments that encode specific protein domains.

The purified polypeptides can be used in *in vitro* binding assays which are well known in the art to identify molecules which bind to the polypeptides. These molecules

include but are not limited to, for e.g., small molecules, molecules from combinatorial libraries, antibodies or other proteins. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

In addition, the peptides of the invention or molecules capable of binding to the peptides may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for SEQ ID NO: 1-1104.

The protein of the invention may also be expressed as a product of transgenic animals, *e.g.*, as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications, in the peptide or DNA sequence, can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, *e.g.*, U.S. Pat. No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein. Regions of the protein that are important for the protein function can be determined by various methods known in the art including the alanine-scanning method which involved systematic substitution of single or strings of amino acids with alanine, followed by testing the resulting alanine-containing variant for biological activity. This type of analysis determines the importance of the substituted amino acid(s) in biological

activity. Regions of the protein that are important for protein function may be determined by the eMATRIX program.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and are useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are encompassed by the present invention.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, Calif., U.S.A. (the MaxBat™ kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (*i.e.*, from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl™ or Cibacrom blue 3GA Sepharose™; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX), or as a His tag. Kits for expression and purification of such fusion

proteins are commercially available from New England BioLab (Beverly, Mass.), Pharmacia (Piscataway, N.J.) and Invitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("FLAG®") is commercially available from Kodak (New Haven, Conn.).

Finally, one or more reverse-phase high performance liquid chromatography (RP- HPLC) steps employing hydrophobic RP-HPLC media, *e.g.*, silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The polypeptides of the invention include analogs (variants). This embraces fragments, as well as peptides in which one or more amino acids has been deleted, inserted, or substituted. Also, analogs of the polypeptides of the invention embrace fusions of the polypeptides or modifications of the polypeptides of the invention, wherein the polypeptide or analog is fused to another moiety or moieties, e.g., targeting moiety or another therapeutic agent. Such analogs may exhibit improved properties such as activity and/or stability. Examples of moieties which may be fused to the polypeptide or an analog include, for example, targeting moieties which provide for the delivery of polypeptide to pancreatic cells, e.g., antibodies to pancreatic cells, antibodies to immune cells such as T-cells, monocytes, dendritic cells, granulocytes, etc., as well as receptor and ligands expressed on pancreatic or immune cells. Other moieties which may be fused to the polypeptide include therapeutic agents which are used for treatment, for example, immunosuppressive drugs such as cyclosporin, SK506, azathioprine, CD3 antibodies and steroids. Also, polypeptides may be fused to immune modulators, and other cytokines such as alpha or beta interferon.

4.4.1 DETERMINING POLYPEPTIDE AND POLYNUCLEOTIDE IDENTITY AND SIMILARITY

Preferred identity and/or similarity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in computer programs including, but are not limited to, the GCG program package, including GAP (Devereux, J., et al., Nucleic Acids Research 12(1):387 (1984); Genetics Computer Group, University of Wisconsin, Madison, WI), BLASTP, BLASTN, BLASTX, FASTA (Altschul, S.F. et al., J. Molec. Biol. 215:403-410 (1990), PSI-BLAST (Altschul S.F. et al., Nucleic Acids Res. vol. 25, pp. 3389-3402, herein incorporated by reference), eMatrix software (Wu et al., J. Comp. Biol., vol. 6, pp. 219-235 (1999), herein incorporated by reference), eMotif software (Nevill-Manning et al, ISMB-97, vol 4, pp. 202-209, herein incorporated by reference) and the Kyte-Doolittle hydrophobocity prediction algorithm (J. Mol Biol, 157, pp. 105-31 (1982), incorporated herein by reference). The BLAST programs are publicly available from the National Center for Biotechnology Information (NCBI) and other sources (BLAST Manual, Altschul, S., et al. NCB NLM NIH Bethesda, MD 20894; Altschul, S., et al., J. Mol. Biol. 215:403-410 (1990).

4.5 GENE THERAPY

Mutations in the polynucleotides of the invention gene may result in loss of normal function of the encoded protein. The invention thus provides gene therapy to restore normal activity of the polypeptides of the invention; or to treat disease states involving polypeptides of the invention. Delivery of a functional gene encoding polypeptides of the invention to appropriate cells is effected *ex vivo*, *in situ*, or *in vivo* by use of vectors, and more particularly viral vectors (e.g., adenovirus, adeno-associated virus, or a retrovirus), or *ex vivo* by use of physical DNA transfer methods (e.g., liposomes or chemical treatments). See, for example, Anderson, Nature, supplement to vol. 392, no. 6679, pp.25-20 (1998). For additional reviews of gene therapy technology see Friedmann, Science, 244: 1275-1281 (1989); Verma, Scientific American: 68-84 (1990); and Miller, Nature, 357: 455-460 (1992). Introduction of any one of the nucleotides of the present invention or a gene encoding the polypeptides of the present invention can also be accomplished with extrachromosomal substrates

(transient expression) or artificial chromosomes (stable expression). Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes. Alternatively, it is contemplated that in other human disease states, preventing the expression of or inhibiting the activity of polypeptides of the invention will be useful in treating the disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of polypeptides of the invention.

Other methods inhibiting expression of a protein include the introduction of antisense molecules to the nucleic acids of the present invention, their complements, or their translated RNA sequences, by methods known in the art. Further, the polypeptides of the present invention can be inhibited by using targeted deletion methods, or the insertion of a negative regulatory element such as a silencer, which is tissue specific.

The present invention still further provides cells genetically engineered *in vivo* to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell which drives expression of the polynucleotides in the cell. These methods can be used to increase or decrease the expression of the polynucleotides of the present invention.

Knowledge of DNA sequences provided by the invention allows for modification of cells to permit, increase, or decrease, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express the protein at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the desired protein encoding sequences. See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., ada, dhfr, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter

DNA. If linked to the desired protein coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the desired protein coding sequences in the cells.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequences include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the protein, or other sequences which alter or improve the function or stability of protein or RNA molecules.

The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, *e.g.,* inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally occurring elements. Here, the naturally occurring sequences are deleted and new sequences are added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes

exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

The gene targeting or gene activation techniques which can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

4.6 TRANSGENIC ANIMALS

In preferred methods to determine biological functions of the polypeptides of the invention in vivo, one or more genes provided by the invention are either over expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals. Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of a promoter of the polynucleotides of the invention is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased protein expression. The homologous promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

The polynucleotides of the present invention also make possible the development, through, e.g., homologous recombination or knock out strategies, of animals that fail to express polypeptides of the invention or that express a variant polypeptide. Such animals are useful as models for studying the *in vivo* activities of polypeptide as well as for studying modulators of the polypeptides of the invention.

In preferred methods to determine biological functions of the polypeptides of the invention *in vivo*, one or more genes provided by the invention are either over expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals. Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of the polynucleotides of the invention promoter is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous

recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased protein expression. The homologous promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

4.7 USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified herein. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA). The mechanism underlying the particular condition or pathology will dictate whether the polypeptides of the invention, the polynucleotides of the invention or modulators (activators or inhibitors) thereof would be beneficial to the subject in need of treatment. Thus, "therapeutic compositions of the invention" include compositions comprising isolated polynucleotides (including recombinant DNA molecules, cloned genes and degenerate variants thereof) or polypeptides of the invention (including full length protein, mature protein and truncations or domains thereof), or compounds and other substances that modulate the overall activity of the target gene products, either at the level of target gene/protein expression or target protein activity. Such modulators include polypeptides, analogs, (variants), including fragments and fusion proteins, antibodies and other binding proteins; chemical compounds that directly or indirectly activate or inhibit the polypeptides of the invention (identified, e.g., via drug screening assays as described herein); antisense polynucleotides and polynucleotides suitable for triple helix formation; and in particular antibodies or other binding partners that specifically recognize one or more epitopes of the polypeptides of the invention.

The polypeptides of the present invention may likewise be involved in cellular activation or in one of the other physiological pathways described herein.

4.7.1 RESEARCH USES AND UTILITIES

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding polypeptide is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Proteins involved in these binding

interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

4.7.2 NUTRITIONAL USES

Polynucleotides and polypeptides of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the polypeptide or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the polypeptide or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

4.7.3 CYTOKINE AND CELL PROLIFERATION/DIFFERENTIATION ACTIVITY

A polypeptide of the present invention may exhibit activity relating to cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor-dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of

therapeutic compositions of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+(preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e, CMK, HUVEC, and Caco. Therapeutic compositions of the invention can be used in the following:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., I. Immunol. 149:3778-3783, 1992; Bowman et al., I. Immunol. 152:1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A. M. and Shevach, E. M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human interleukin-γ, Schreiber, R. D. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L. S. and Lipsky, P. E. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6--Nordan, R. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Aced. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11--Bennett, F.,

Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9--Ciarletta, A., Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

4.7.4 STEM CELL GROWTH FACTOR ACTIVITY

A polypeptide of the present invention may exhibit stem cell growth factor activity and be involved in the proliferation, differentiation and survival of pluripotent and totipotent stem cells including primordial germ cells, embryonic stem cells, hematopoietic stem cells and/or germ line stem cells. Administration of the polypeptide of the invention to stem cells *in vivo* or *ex vivo* is expected to maintain and expand cell populations in a totipotential or pluripotential state which would be useful for re-engineering damaged or diseased tissues, transplantation, manufacture of bio-pharmaceuticals and the development of bio-sensors. The ability to produce large quantities of human cells has important working applications for the production of human proteins which currently must be obtained from non-human sources or donors, implantation of cells to treat diseases such as Parkinson's, Alzheimer's and other neurodegenerative diseases; tissues for grafting such as bone marrow, skin, cartilage, tendons, bone, muscle (including cardiac muscle), blood vessels, cornea, neural cells,

gastrointestinal cells and others; and organs for transplantation such as kidney, liver, pancreas (including islet cells), heart and lung.

It is contemplated that multiple different exogenous growth factors and/or cytokines may be administered in combination with the polypeptide of the invention to achieve the desired effect, including any of the growth factors listed herein, other stem cell maintenance factors, and specifically including stem cell factor (SCF), leukemia inhibitory factor (LIF), Flt-3 ligand (Flt-3L), any of the interleukins, recombinant soluble IL-6 receptor fused to IL-6, macrophage inflammatory protein 1-alpha (MIP-1-alpha), G-CSF, GM-CSF, thrombopoietin (TPO), platelet factor 4 (PF-4), platelet-derived growth factor (PDGF), neural growth factors and basic fibroblast growth factor (bFGF).

Since totipotent stem cells can give rise to virtually any mature cell type, expansion of these cells in culture will facilitate the production of large quantities of mature cells. Techniques for culturing stem cells are known in the art and administration of polypeptides of the invention, optionally with other growth factors and/or cytokines, is expected to enhance the survival and proliferation of the stem cell populations. This can be accomplished by direct administration of the polypeptide of the invention to the culture medium. Alternatively, stroma cells transfected with a polynucleotide that encodes for the polypeptide of the invention can be used as a feeder layer for the stem cell populations in culture or in vivo. Stromal support cells for feeder layers may include embryonic bone marrow fibroblasts, bone marrow stromal cells, fetal liver cells, or cultured embryonic fibroblasts (see U.S. Patent No. 5,690,926).

Stem cells themselves can be transfected with a polynucleotide of the invention to induce autocrine expression of the polypeptide of the invention. This will allow for generation of undifferentiated totipotential/pluripotential stem cell lines that are useful as is or that can then be differentiated into the desired mature cell types. These stable cell lines can also serve as a source of undifferentiated totipotential/pluripotential mRNA to create cDNA libraries and templates for polymerase chain reaction experiments. These studies would allow for the isolation and identification of

differentially expressed genes in stem cell populations that regulate stem cell proliferation and/or maintenance.

Expansion and maintenance of totipotent stem cell populations will be useful in the treatment of many pathological conditions. For example, polypeptides of the present invention may be used to manipulate stem cells in culture to give rise to neuroepithelial cells that can be used to augment or replace cells damaged by illness, autoimmune disease, accidental damage or genetic disorders. The polypeptide of the invention may be useful for inducing the proliferation of neural cells and for the regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders which involve degeneration, death or trauma to neural cells or nerve tissue. In addition, the expanded stem cell populations can also be genetically altered for gene therapy purposes and to decrease host rejection of replacement tissues after grafting or implantation.

Expression of the polypeptide of the invention and its effect on stem cells can also be manipulated to achieve controlled differentiation of the stem cells into more differentiated cell types. A broadly applicable method of obtaining pure populations of a specific differentiated cell type from undifferentiated stem cell populations involves the use of a cell-type specific promoter driving a selectable marker. The selectable marker allows only cells of the desired type to survive. For example, stem cells can be induced to differentiate into cardiomyocytes (Wobus et al., Differentiation, 48: 173-182, (1991); Klug et al., J. Clin. Invest., 98(1): 216-224, (1998)) or skeletal muscle cells (Browder, L. W. In: *Principles of Tissue Engineering eds.* Lanza et al., Academic Press (1997)). Alternatively, directed differentiation of stem cells can be accomplished by culturing the stem cells in the presence of a differentiation factor such as retinoic acid and an antagonist of the polypeptide of the invention which would inhibit the effects of endogenous stem cell factor activity and allow differentiation to proceed.

In vitro cultures of stem cells can be used to determine if the polypeptide of the invention exhibits stem cell growth factor activity. Stem cells are isolated from any one

of various cell sources (including hematopoietic stem cells and embryonic stem cells) and cultured on a feeder layer, as described by Thompson et al. Proc. Natl. Acad. Sci, U.S.A., 92: 7844-7848 (1995), in the presence of the polypeptide of the invention alone or in combination with other growth factors or cytokines. The ability of the polypeptide of the invention to induce stem cells proliferation is determined by colony formation on semi-solid support e.g. as described by Bernstein et al., Blood, 77: 2316-2321 (1991).

4.7.5 HEMATOPOIESIS REGULATING ACTIVITY

A polypeptide of the present invention may be involved in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell disorders. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone

marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

Therapeutic compositions of the invention can be used in the following:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M. G. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, N.Y. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I. K. and Briddell, R. A. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, N.Y. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R. E. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, N.Y. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, N.Y. 1994; Long term culture initiating cell assay, Sutherland, H. J. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, N.Y. 1994.

4.7.6 TISSUE GROWTH ACTIVITY

A polypeptide of the present invention also may be involved in bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as in wound healing and tissue repair and replacement, and in healing of burns, incisions and ulcers.

A polypeptide of the present invention which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Compositions of a polypeptide, antibody, binding partner, or other modulator of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A polypeptide of this invention may also be involved in attracting bone-forming cells, stimulating growth of bone-forming cells, or inducing differentiation of progenitors of bone-forming cells. Treatment of osteoporosis, osteoarthritis, bone degenerative disorders, or periodontal disease, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes may also be possible using the composition of the invention.

Another category of tissue regeneration activity that may involve the polypeptide of the present invention is tendon/ligament formation. Induction of tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments.

The compositions of the present invention may provide environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The compositions of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a composition may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a composition of the invention.

Compositions of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

Compositions of the present invention may also be involved in the generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation

of fibrotic scarring may allow normal tissue to regenerate. A polypeptide of the present invention may also exhibit angiogenic activity.

A composition of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A composition of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Therapeutic compositions of the invention can be used in the following:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, H. I. and Rovee, D. T., eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

4.7.7 IMMUNE STIMULATING OR SUPPRESSING ACTIVITY

A polypeptide of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A polynucleotide of the invention can encode a polypeptide exhibiting such activities. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses,

herpes viruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, proteins of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein (or antagonists thereof, including antibodies) of the present invention may also to be useful in the treatment of allergic reactions and conditions (*e.g.*, anaphylaxis, serum sickness, drug reactions, food allergies, insect venom allergies, mastocytosis, allergic rhinitis, hypersensitivity pneumonitis, urticaria, angioedema, eczema, atopic dermatitis, allergic contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, allergic conjunctivitis, atopic keratoconjunctivitis, venereal keratoconjunctivitis, giant papillary conjunctivitis and contact allergies), such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein (or antagonists thereof) of the present invention. The therapeutic effects of the polypeptides or antagonists thereof on allergic reactions can be evaluated by in vivo animals models such as the cumulative contact enhancement test (Lastbom et al., Toxicology 125: 59-66, 1998), skin prick test (Hoffmann et al., Allergy 54: 446-54, 1999), guinea pig skin sensitization test (Vohr et al., Arch. Toxocol. 73: 501-9), and murine local lymph node assay (Kimber et al., J. Toxicol. Environ. Health 53: 563-79).

Using the proteins of the invention it may also be possible to modulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both.

Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a therapeutic composition of the invention may prevent cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, a lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular therapeutic compositions in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York,

1989, pp. 846-847) can be used to determine the effect of therapeutic compositions of the invention on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block stimulation of T cells can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (e.g., a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response may be useful in cases of viral infection, including systemic viral diseases such as influenza, the common cold, and encephalitis.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient,

transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

A polypeptide of the present invention may provide the necessary stimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient mounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I alpha chain protein and β_2 microglobulin protein or an MHC class II alpha chain protein and an MHC class II beta chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J.

Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., I. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bowman et al., J. Virology 61:1992-1998; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J. J. and Brunswick, M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate

lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

4.7.8 ACTIVIN/INHIBIN ACTIVITY

A polypeptide of the present invention may also exhibit activin- or inhibin-related activities. A polynucleotide of the invention may encode a polypeptide exhibiting such characteristics. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a polypeptide of the present invention, alone or in heterodimers with a member of the inhibin family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the polypeptide of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, U.S. Pat. No. 4,798,885. A polypeptide of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as, but not limited to, cows, sheep and pigs.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods.

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

4.7.9 CHEMOTACTIC/CHEMOKINETIC ACTIVITY

A polypeptide of the present invention may be involved in chemotactic or chemokinetic activity for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Chemotactic and chemokinetic receptor activation can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic compositions (e.g. proteins, antibodies, binding partners, or modulators of the invention) provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

Therapeutic compositions of the invention can be used in the following:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for

movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Marguiles, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

4.7.10 HEMOSTATIC AND THROMBOLYTIC ACTIVITY

A polypeptide of the invention may also be involved in hemostatis or thrombolysis or thrombosis. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Compositions may be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A composition of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

Therapeutic compositions of the invention can be used in the following:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

4.7.11 CANCER DIAGNOSIS AND THERAPY

Polypeptides of the invention may be involved in cancer cell generation, proliferation or metastasis. Detection of the presence or amount of polynucleotides or polypeptides of the invention may be useful for the diagnosis and/or prognosis of one or more types of cancer. For example, the presence or increased expression of a polynucleotide/polypeptide of the invention may indicate a hereditary risk of cancer, a

precancerous condition, or an ongoing malignancy. Conversely, a defect in the gene or absence of the polypeptide may be associated with a cancer condition. Identification of single nucleotide polymorphisms associated with cancer or a predisposition to cancer may also be useful for diagnosis or prognosis.

Cancer treatments promote tumor regression by inhibiting tumor cell proliferation, inhibiting angiogenesis (growth of new blood vessels that is necessary to support tumor growth) and/or prohibiting metastasis by reducing tumor cell motility or invasiveness. Therapeutic compositions of the invention may be effective in adult and pediatric oncology including in solid phase tumors/malignancies, locally advanced tumors, human soft tissue sarcomas, metastatic cancer, including lymphatic metastases, blood cell malignancies including multiple myeloma, acute and chronic leukemias, and lymphomas, head and neck cancers including mouth cancer, larynx cancer and thyroid cancer, lung cancers including small cell carcinoma and non-small cell cancers, breast cancers including small cell carcinoma and ductal carcinoma, gastrointestinal cancers including esophageal cancer, stomach cancer, colon cancer, colorectal cancer and polyps associated with colorectal neoplasia, pancreatic cancers, liver cancer, urologic cancers including bladder cancer and prostate cancer, malignancies of the female genital tract including ovarian carcinoma, uterine (including endometrial) cancers, and solid tumor in the ovarian follicle, kidney cancers including renal cell carcinoma, brain cancers including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, metastatic tumor cell invasion in the central nervous system, bone cancers including osteomas, skin cancers including malignant melanoma, tumor progression of human skin keratinocytes, squamous cell carcinoma, basal cell carcinoma, hemangiopericytoma and Karposi's sarcoma.

Polypeptides, polynucleotides, or modulators of polypeptides of the invention (including inhibitors and stimulators of the biological activity of the polypeptide of the invention) may be administered to treat cancer. Therapeutic compositions can be administered in therapeutically effective dosages alone or in combination with adjuvant cancer therapy such as surgery, chemotherapy, radiotherapy, thermotherapy, and laser therapy, and may provide a beneficial effect, e.g. reducing tumor size, slowing rate of

tumor growth, inhibiting metastasis, or otherwise improving overall clinical condition, without necessarily eradicating the cancer.

The composition can also be administered in therapeutically effective amounts as a portion of an anti-cancer cocktail. An anti-cancer cocktail is a mixture of the polypeptide or modulator of the invention with one or more anti-cancer drugs in addition to a pharmaceutically acceptable carrier for delivery. The use of anti-cancer cocktails as a cancer treatment is routine. Anti-cancer drugs that are well known in the art and can be used as a treatment in combination with the polypeptide or modulator of the invention include: Actinomycin D, Aminoglutethimide, Asparaginase, Bleomycin, Busulfan, Carboplatin, Carmustine, Chlorambucil, Cisplatin (cis-DDP), Cyclophosphamide, Cytarabine HCl (Cytosine arabinoside), Dacarbazine, Dactinomycin, Daunorubicin HCl, Doxorubicin HCl, Estramustine phosphate sodium, Etoposide (V16-213), Floxuridine, 5-Fluorouracil (5-Fu), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alpha-2a, Interferon Alpha-2b, Leuprolide acetate (LHRH-releasing factor analog), Lomustine, Mechlorethamine HCl (nitrogen mustard), Melphalan, Mercaptopurine, Mesna, Methotrexate (MTX), Mitomycin, Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl, Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine sulfate, Vincristine sulfate, Amsacrine, Azacitidine, Hexamethylmelamine, Interleukin-2, Mitoguazone, Pentostatin, Semustine, Teniposide, and Vindesine sulfate.

In addition, therapeutic compositions of the invention may be used for prophylactic treatment of cancer. There are hereditary conditions and/or environmental situations (e.g. exposure to carcinogens) known in the art that predispose an individual to developing cancers. Under these circumstances, it may be beneficial to treat these individuals with therapeutically effective doses of the polypeptide of the invention to reduce the risk of developing cancers.

In vitro models can be used to determine the effective doses of the polypeptide of the invention as a potential cancer treatment. These *in vitro* models include proliferation assays of cultured tumor cells, growth of cultured tumor cells in soft agar (see Freshney, (1987) Culture of Animal Cells: A Manual of Basic Technique, Wily-

Liss, New York, NY Ch 18 and Ch 21), tumor systems in nude mice as described in Giovanella et al., J. Natl. Can. Inst., 52: 921-30 (1974), mobility and invasive potential of tumor cells in Boyden Chamber assays as described in Pilkington et al., Anticancer Res., 17: 4107-9 (1997), and angiogenesis assays such as induction of vascularization of the chick chorioallantoic membrane or induction of vascular endothelial cell migration as described in Ribatta et al., Intl. J. Dev. Biol., 40: 1189-97 (1999) and Li et al., Clin. Exp. Metastasis, 17:423-9 (1999), respectively. Suitable tumor cells lines are available, e.g. from American Type Tissue Culture Collection catalogs.

4.7.12 RECEPTOR/LIGAND ACTIVITY

A polypeptide of the present invention may also demonstrate activity as receptor, receptor ligand or inhibitor or agonist of receptor/ligand interactions. A polynucleotide of the invention can encode a polypeptide exhibiting such characteristics. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses. Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley- Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1- 7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA

84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

By way of example, the polypeptides of the invention may be used as a receptor for a ligand(s) thereby transmitting the biological activity of that ligand(s). Ligands may be identified through binding assays, affinity chromatography, dihybrid screening assays, BIAcore assays, gel overlay assays, or other methods known in the art.

Studies characterizing drugs or proteins as agonist or antagonist or partial agonists or a partial antagonist require the use of other proteins as competing ligands. The polypeptides of the present invention or ligand(s) thereof may be labeled by being coupled to radioisotopes, colorimetric molecules or a toxin molecules by conventional methods. ("Guide to Protein Purification" Murray P. Deutscher (ed) Methods in Enzymology Vol. 182 (1990) Academic Press, Inc. San Diego). Examples of radioisotopes include, but are not limited to, tritium and carbon-14 . Examples of colorimetric molecules include, but are not limited to, fluorescent molecules such as fluorescamine, or rhodamine or other colorimetric molecules. Examples of toxins include, but are not limited, to ricin.

4.7.13 DRUG SCREENING

This invention is particularly useful for screening chemical compounds by using the novel polypeptides or binding fragments thereof in any of a variety of drug screening techniques. The polypeptides or fragments employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or a fragment thereof. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between polypeptides of the invention or fragments and the agent being

tested or examine the diminution in complex formation between the novel polypeptides and an appropriate cell line, which are well known in the art.

Sources for test compounds that may be screened for ability to bind to or modulate (i.e., increase or decrease) the activity of polypeptides of the invention include (1) inorganic and organic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of either random or mimetic peptides, oligonucleotides or organic molecules.

Chemical libraries may be readily synthesized or purchased from a number of commercial sources, and may include structural analogs of known compounds or compounds that are identified as "hits" or "leads" via natural product screening.

The sources of natural product libraries are microorganisms (including bacteria and fungi), animals, plants or other vegetation, or marine organisms, and libraries of mixtures for screening may be created by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of the organisms themselves. Natural product libraries include polyketides, non-ribosomal peptides, and (non-naturally occurring) variants thereof. For a review, see *Science 282*:63-68 (1998).

Combinatorial libraries are composed of large numbers of peptides, oligonucleotides or organic compounds and can be readily prepared by traditional automated synthesis methods, PCR, cloning or proprietary synthetic methods. Of particular interest are peptide and oligonucleotide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, *Curr. Opin. Biotechnol.* 8:701-707 (1997). For reviews and examples of peptidomimetic libraries, see Al-Obeidi et al., *Mol. Biotechnol*, 9(3):205-23 (1998); Hruby et al., *Curr Opin Chem Biol*, 1(1):114-19 (1997); Dorner et al., *Bioorg Med Chem*, 4(5):709-15 (1996) (alkylated dipeptides).

Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the

"hit" to bind a polypeptide of the invention. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

The binding molecules thus identified may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells such as radioisotopes. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for a polypeptide of the invention. Alternatively, the binding molecules may be complexed with imaging agents for targeting and imaging purposes.

4.7.14 ASSAY FOR RECEPTOR ACTIVITY

The invention also provides methods to detect specific binding of a polypeptide e.g. a ligand or a receptor. The art provides numerous assays particularly useful for identifying previously unknown binding partners for receptor polypeptides of the invention. For example, expression cloning using mammalian or bacterial cells, or dihybrid screening assays can be used to identify polynucleotides encoding binding partners. As another example, affinity chromatography with the appropriate immobilized polypeptide of the invention can be used to isolate polypeptides that recognize and bind polypeptides of the invention. There are a number of different libraries used for the identification of compounds, and in particular small molecules, that modulate (*i.e.,* increase or decrease) biological activity of a polypeptide of the invention. Ligands for receptor polypeptides of the invention can also be identified by adding exogenous ligands, or cocktails of ligands to two cells populations that are genetically identical except for the expression of the receptor of the invention: one cell population expresses the receptor of the invention whereas the other does not. The response of the two cell populations to the addition of ligands(s) are then compared. Alternatively, an expression library can be co-expressed with the polypeptide of the invention in cells and assayed for an autocrine response to identify potential ligand(s).

As still another example, BIAcore assays, gel overlay assays, or other methods known in the art can be used to identify binding partner polypeptides, including, (1) organic and inorganic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules.

The role of downstream intracellular signaling molecules in the signaling cascade of the polypeptide of the invention can be determined. For example, a chimeric protein in which the cytoplasmic domain of the polypeptide of the invention is fused to the extracellular portion of a protein, whose ligand has been identified, is produced in a host cell. The cell is then incubated with the ligand specific for the extracellular portion of the chimeric protein, thereby activating the chimeric receptor. Known downstream proteins involved in intracellular signaling can then be assayed for expected modifications i.e. phosphorylation. Other methods known to those in the art can also be used to identify signaling molecules involved in receptor activity.

4.7.15 ANTI-INFLAMMATORY ACTIVITY

Compositions of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Compositions with such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation intimation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Compositions of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material. Compositions of this invention

may be utilized to prevent or treat conditions such as, but not limited to, sepsis, acute pancreatitis, endotoxin shock, cytokine induced shock, rheumatoid arthritis, chronic inflammatory arthritis, pancreatic cell damage from diabetes mellitus type 1, graft versus host disease, inflammatory bowel disease, inflamation associated with pulmonary disease, other autoimmune disease or inflammatory disease, an antiproliferative agent such as for acute or chronic mylegenous leukemia or in the prevention of premature labor secondary to intrauterine infections.

4.7.16 LEUKEMIAS

Leukemias and related disorders may be treated or prevented by administration of a therapeutic that promotes or inhibits function of the polynucleotides and/or polypeptides of the invention. Such leukemias and related disorders include but are not limited to acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia, chronic leukemia, chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia (for a review of such disorders, see Fishman et al., 1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia).

4.7.17 NERVOUS SYSTEM DISORDERS

Nervous system disorders, involving cell types which can be tested for efficacy of intervention with compounds that modulate the activity of the polynucleotides and/or polypeptides of the invention, and which can be treated upon thus observing an indication of therapeutic utility, include but are not limited to nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the invention include but are not limited to the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems:

(i) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries;

(ii) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia;

(iii) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, syphilis;

(iv) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis;

(v) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration;

(vi) neurological lesions associated with systemic diseases including but not limited to diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis;

(vii) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and

(viii) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including but not limited to multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

Therapeutics which are useful according to the invention for treatment of a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, therapeutics which elicit any of the following effects may be useful according to the invention:

(i) increased survival time of neurons in culture;

(ii) increased sprouting of neurons in culture or in vivo;

(iii) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or

(iv) decreased symptoms of neuron dysfunction in vivo.

Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may be measured by the method set forth in Arakawa et al. (1990, J. Neurosci. 10:3507-3515); increased sprouting of neurons may be detected by methods set forth in Pestronk et al. (1980, Exp. Neurol. 70:65-82) or Brown et al. (1981, Ann. Rev. Neurosci. 4:17-42); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, *etc.*, depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, *e.g.*, weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include but are not limited to disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including but not limited to progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

4.7.18 OTHER ACTIVITIES

A polypeptide of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, co-factors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

4.7.19 IDENTIFICATION OF POLYMORPHISMS

The demonstration of polymorphisms makes possible the identification of such polymorphisms in human subjects and the pharmacogenetic use of this information for diagnosis and treatment. Such polymorphisms may be associated with, e.g., differential predisposition or susceptibility to various disease states (such as disorders involving inflammation or immune response) or a differential response to drug administration,

and this genetic information can be used to tailor preventive or therapeutic treatment appropriately. For example, the existence of a polymorphism associated with a predisposition to inflammation or autoimmune disease makes possible the diagnosis of this condition in humans by identifying the presence of the polymorphism.

Polymorphisms can be identified in a variety of ways known in the art which all generally involve obtaining a sample from a patient, analyzing DNA from the sample, optionally involving isolation or amplification of the DNA, and identifying the presence of the polymorphism in the DNA. For example, PCR may be used to amplify an appropriate fragment of genomic DNA which may then be sequenced. Alternatively, the DNA may be subjected to allele-specific oligonucleotide hybridization (in which appropriate oligonucleotides are hybridized to the DNA under conditions permitting detection of a single base mismatch) or to a single nucleotide extension assay (in which an oligonucleotide that hybridizes immediately adjacent to the position of the polymorphism is extended with one or more labeled nucleotides). In addition, traditional restriction fragment length polymorphism analysis (using restriction enzymes that provide differential digestion of the genomic DNA depending on the presence or absence of the polymorphism) may be performed. Arrays with nucleotide sequences of the present invention can be used to detect polymorphisms. The array can comprise modified nucleotide sequences of the present invention in order to detect the nucleotide sequences of the present invention. In the alternative, any one of the nucleotide sequences of the present invention can be placed on the array to detect changes from those sequences.

Alternatively a polymorphism resulting in a change in the amino acid sequence could also be detected by detecting a corresponding change in amino acid sequence of the protein, e.g., by an antibody specific to the variant sequence.

4.7.20 ARTHRITIS AND INFLAMMATION

The immunosuppressive effects of the compositions of the invention against rheumatoid arthritis is determined in an experimental animal model system. The experimental model system is adjuvant induced arthritis in rats, and the protocol is

described by J. Holoshitz, et at., 1983, Science, 219:56, or by B. Waksman et al., 1963, Int. Arch. Allergy Appl. Immunol., 23:129. Induction of the disease can be caused by a single injection, generally intradermally, of a suspension of killed Mycobacterium tuberculosis in complete Freund's adjuvant (CFA). The route of injection can vary, but rats may be injected at the base of the tail with an adjuvant mixture. The polypeptide is administered in phosphate buffered solution (PBS) at a dose of about 1-5 mg/kg. The control consists of administering PBS only.

The procedure for testing the effects of the test compound would consist of intradermally injecting killed Mycobacterium tuberculosis in CFA followed by immediately administering the test compound and subsequent treatment every other day until day 24. At 14, 15, 18, 20, 22, and 24 days after injection of Mycobacterium CFA, an overall arthritis score may be obtained as described by J. Holoskitz above. An analysis of the data would reveal that the test compound would have a dramatic affect on the swelling of the joints as measured by a decrease of the arthritis score.

4.8 THERAPEUTIC METHODS

The compositions (including polypeptide fragments, analogs, variants and antibodies or other binding partners or modulators including antisense polynucleotides) of the invention have numerous applications in a variety of therapeutic methods. Examples of therapeutic applications include, but are not limited to, those exemplified herein.

4.8.1 EXAMPLE

One embodiment of the invention is the administration of an effective amount of the polypeptides or other composition of the invention to individuals affected by a disease or disorder that can be modulated by regulating the peptides of the invention. While the mode of administration is not particularly important, parenteral administration is preferred. An exemplary mode of administration is to deliver an intravenous bolus. The dosage of the polypeptides or other composition of the

invention will normally be determined by the prescribing physician. It is to be expected that the dosage will vary according to the age, weight, condition and response of the individual patient. Typically, the amount of polypeptide administered per dose will be in the range of about 0.01μg/kg to 100 mg/kg of body weight, with the preferred dose being about 0.1μg/kg to 10 mg/kg of patient body weight. For parenteral administration, polypeptides of the invention will be formulated in an injectable form combined with a pharmaceutically acceptable parenteral vehicle. Such vehicles are well known in the art and examples include water, saline, Ringer's solution, dextrose solution, and solutions consisting of small amounts of the human serum albumin. The vehicle may contain minor amounts of additives that maintain the isotonicity and stability of the polypeptide or other active ingredient. The preparation of such solutions is within the skill of the art.

4.9 PHARMACEUTICAL FORMULATIONS AND ROUTES OF ADMINISTRATION

A protein or other composition of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources and including antibodies and other binding partners of the polypeptides of the invention) may be administered to a patient in need, by itself, or in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s) at doses to treat or ameliorate a variety of disorders. Such a composition may optionally contain (in addition to protein or other active ingredient and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF,

Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the disease or disorder in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), insulin-like growth factor (IGF), as well as cytokines described herein.

The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or other active ingredient or complement its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein or other active ingredient of the invention, or to minimize side effects. Conversely, protein or other active ingredient of the present invention may be included in formulations of the particular clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti- inflammatory agent to minimize side effects of the clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent (such as IL-1Ra, IL-1 Hy1, IL-1 Hy2, anti-TNF, corticosteroids, immunosuppressive agents). A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

As an alternative to being included in a pharmaceutical composition of the invention including a first protein, a second protein or a therapeutic agent may be concurrently administered with the first protein (e.g., at the same time, or at differing times provided that therapeutic concentrations of the combination of agents is achieved at the treatment site). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition. A therapeutically effective dose further refers to that amount of the compound sufficient to result in amelioration of symptoms, *e.g.*, treatment, healing, prevention or amelioration of the relevant medical

condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, a therapeutically effective dose refers to that ingredient alone. When applied to a combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein or other active ingredient of the present invention is administered to a mammal having a condition to be treated. Protein or other active ingredient of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co- administered with one or more cytokines, lymphokines or other hematopoietic factors, protein or other active ingredient of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein or other active ingredient of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

4.9.1 ROUTES OF ADMINISTRATION

Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. Administration of protein or other active ingredient of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or

cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a arthritic joints or in fibrotic tissue, often in a depot or sustained release formulation. In order to prevent the scarring process frequently occurring as complication of glaucoma surgery, the compounds may be administered topically, for example, as eye drops. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a specific antibody, targeting, for example, arthritic or fibrotic tissue. The liposomes will be targeted to and taken up selectively by the afflicted tissue.

The polypeptides of the invention are administered by any route that delivers an effective dosage to the desired site of action. The determination of a suitable route of administration and an effective dosage for a particular indication is within the level of skill in the art. Preferably for wound treatment, one administers the therapeutic compound directly to the site. Suitable dosage ranges for the polypeptides of the invention can be extrapolated from these dosages or from similar studies in appropriate animal models. Dosages can then be adjusted as necessary by the clinician to provide maximal therapeutic benefit.

4.9.2 COMPOSITIONS/FORMULATIONS

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. These pharmaceutical compositions may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of protein or other active ingredient of the present

invention is administered orally, protein or other active ingredient of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein or other active ingredient of the present invention, and preferably from about 25 to 90% protein or other active ingredient of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein or other active ingredient of the present invention, and preferably from about 1 to 50% protein or other active ingredient of the present invention.

When a therapeutically effective amount of protein or other active ingredient of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein or other active ingredient of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein or other active ingredient solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein or other active ingredient of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art. For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For

transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained from a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such

administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch. The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides. In addition to the formulations described

previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a co-solvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The co-solvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose. Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological

stability of the therapeutic reagent, additional strategies for protein or other active ingredient stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Many of the active ingredients of the invention may be provided as salts with pharmaceutically compatible counter ions. Such pharmaceutically acceptable base addition salts are those salts which retain the biological effectiveness and properties of the free acids and which are obtained by reaction with inorganic or organic bases such as sodium hydroxide, magnesium hydroxide, ammonia, trialkylamine, dialkylamine, monoalkylamine, dibasic amino acids, sodium acetate, potassium benzoate, triethanol amine and the like.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) or other active ingredient(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without

limitation, monoglycerides, diglycerides, sulfatides, lysolecithins, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent Nos. 4,235,871; 4,501,728; 4,837,028; and 4,737,323, all of which are incorporated herein by reference.

The amount of protein or other active ingredient of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein or other active ingredient of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein or other active ingredient of the present invention and observe the patient's response. Larger doses of protein or other active ingredient of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μg to about 100 mg (preferably about 0.1 μg to about 10 mg, more preferably about 0.1 μg to about 1 mg) of protein or other active ingredient of the present invention per kg body weight. For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein or other active ingredient of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would

include a matrix capable of delivering the protein-containing or other active ingredient-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalcium phosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability. Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent

useful herein is 0.5-20 wt %, preferably 1-10 wt % based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells. In further compositions, proteins or other active ingredients of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins or other active ingredients of the present invention. The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, *e.g.*, amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (*e.g.*, bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either in vivo or ex vivo into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA). Cells may also be

cultured ex vivo in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced in vivo for therapeutic purposes.

4.9.3 EFFECTIVE DOSAGE

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from appropriate in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that can be used to more accurately determine useful doses in humans. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of the protein's biological activity). Such information can be used to more accurately determine useful doses in humans.

A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies

preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. See, *e.g.*, Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1. Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the desired effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

An exemplary dosage regimen for polypeptides or other compositions of the invention will be in the range of about 0.01 μg/kg to 100 mg/kg of body weight daily, with the preferred dose being about 0.1 μg/kg to 25 mg/kg of patient body weight daily, varying in adults and children. Dosing may be once daily, or equivalent doses may be delivered at longer or shorter intervals.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's age and weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

4.9.4 PACKAGING

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

4.10 ANTIBODIES

Another aspect of the invention is an antibody that specifically binds the polypeptide of the invention. Such antibodies include monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, and complementary determining region (CDR)-grafted antibodies, including compounds which include CDR and/or antigen-binding sequences, which specifically recognize a polypeptide of the invention. Preferred antibodies of the invention are human antibodies which are produced and identified according to methods described in WO93/11236, published June 20, 1993, which is incorporated herein by reference in its entirety. Antibody fragments, including Fab, Fab´, F(ab´)$_2$, and F$_v$, are also provided by the invention. The term "specific for" indicates that the variable regions of the antibodies of the invention recognize and bind polypeptides of the invention exclusively (*i.e.*, able to distinguish the polypeptide of the invention from other similar polypeptides despite sequence identity, homology, or similarity found in the family of polypeptides), but may also interact with other proteins (for example, *S. aureus* protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow et al. (Eds), Antibodies A Laboratory Manual; Cold Spring Harbor Laboratory; Cold Spring Harbor , NY (1988), Chapter 6. Antibodies that recognize and bind fragments of the polypeptides of the invention are also contemplated, provided that the antibodies are first and foremost specific for, as defined above, full length polypeptides of the invention. As with antibodies that are specific for full length polypeptides of the invention, antibodies of the invention that recognize fragments are those which can

distinguish polypeptides from the same family of polypeptides despite inherent sequence identity, homology, or similarity found in the family of proteins. Antibodies of the invention can be produced using any method well known and routinely practiced in the art.

Non-human antibodies may be humanized by any methods known in the art. In one method, the non-human CDRs are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity.

Antibodies of the invention are useful for, for example, therapeutic purposes (by modulating activity of a polypeptide of the invention), diagnostic purposes to detect or quantitate a polypeptide of the invention, as well as purification of a polypeptide of the invention. Kits comprising an antibody of the invention for any of the purposes described herein are also comprehended. In general, a kit of the invention also includes a control antigen for which the antibody is immunospecific. The invention further provides a hybridoma that produces an antibody according to the invention. Antibodies of the invention are useful for detection and/or purification of the polypeptides of the invention.

Polypeptides of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R. P. Merrifield, J. Amer. Chem. Soc. 85, 2149-2154 (1963); J. L. Krstenansky, et al., FEBS Lett. 211, 10 (1987).

Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or

leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein. In general, techniques for preparing polyclonal and monoclonal antibodies as well as hybridomas capable of producing the desired antibody are well known in the art (Campbell, A.M., Monoclonal Antibodies Technology: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1984); St. Groth et al., J. Immunol. 35:1-21 (1990); Kohler and Milstein, Nature 256:495-497 (1975)), the trioma technique, the human B-cell hybridoma technique (Kozbor et al., Immunology Today 4:72 (1983); Cole et al., in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. (1985), pp. 77-96).

Any animal (mouse, rabbit, *etc.*) which is known to produce antibodies can be immunized with a peptide or polypeptide of the invention. Methods for immunization are well known in the art. Such methods include subcutaneous or intraperitoneal injection of the polypeptide. One skilled in the art will recognize that the amount of the protein encoded by the ORF of the present invention used for immunization will vary based on the animal which is immunized, the antigenicity of the peptide and the site of injection. The protein that is used as an immunogen may be modified or administered in an adjuvant in order to increase the protein's antigenicity. Methods of increasing the antigenicity of a protein are well known in the art and include, but are not limited to, coupling the antigen with a heterologous protein (such as globulin or -galactosidase) or through the inclusion of an adjuvant during immunization.

For monoclonal antibodies, spleen cells from the immunized animals are removed, fused with myeloma cells, such as SP2/0-Ag14 myeloma cells, and allowed to become monoclonal antibody producing hybridoma cells. Any one of a number of methods well known in the art can be used to identify the hybridoma cell which produces an antibody with the desired characteristics. These include screening the hybridomas with an ELISA assay, Western blot analysis, or radioimmunoassay (Lutz et al., Exp. Cell Research. 175:109-124 (1988)). Hybridomas secreting the desired antibodies are cloned and the class and subclass is determined using procedures known

in the art (Campbell, A.M., Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1984)). Techniques described for the production of single chain antibodies (U.S. Patent 4,946,778) can be adapted to produce single chain antibodies to proteins of the present invention.

For polyclonal antibodies, antibody-containing antiserum is isolated from the immunized animal and is screened for the presence of antibodies with the desired specificity using one of the above-described procedures. The present invention further provides the above- described antibodies in delectably labeled form. Antibodies can be delectably labeled through the use of radioisotopes, affinity labels (such as biotin, avidin, etc.), enzymatic labels (such as horseradish peroxidase, alkaline phosphatase, etc.) fluorescent labels (such as FITC or rhodamine, etc.), paramagnetic atoms, etc. Procedures for accomplishing such labeling are well-known in the art, for example, see (Sternberger, L.A. et al., J. Histochem. Cytochem. 18:315 (1970); Bayer, E.A. et al., Meth. Enzym. 62:308 (1979); Engval, E. et al., Immunol. 109:129 (1972); Goding, J.W. J. Immunol. Meth. 13:215 (1976)).

The labeled antibodies of the present invention can be used for *in vitro*, *in vivo*, and *in situ* assays to identify cells or tissues in which a fragment of the polypeptide of interest is expressed. The antibodies may also be used directly in therapies or other diagnostics. The present invention further provides the above-described antibodies immobilized on a solid support. Examples of such solid supports include plastics such as polycarbonate, complex carbohydrates such as agarose and Sepharose®, acrylic resins and such as polyacrylamide and latex beads. Techniques for coupling antibodies to such solid supports are well known in the art (Weir, D.M. et al., "Handbook of Experimental Immunology" 4th Ed., Blackwell Scientific Publications, Oxford, England, Chapter 10 (1986); Jacoby, W.D. et al., Meth. Enzym. 34 Academic Press, N.Y. (1974)). The immobilized antibodies of the present invention can be used for *in vitro*, *in vivo*, and *in situ* assays as well as for immuno-affinity purification of the proteins of the present invention.

4.11 COMPUTER READABLE SEQUENCES

In one application of this embodiment, a nucleotide sequence of the present invention can be recorded on computer readable media. As used herein, "computer readable media" refers to any medium which can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. A skilled artisan can readily appreciate how any of the presently known computer readable mediums can be used to create a manufacture comprising computer readable medium having recorded thereon a nucleotide sequence of the present invention. As used herein, "recorded" refers to a process for storing information on computer readable medium. A skilled artisan can readily adopt any of the presently known methods for recording information on computer readable medium to generate manufactures comprising the nucleotide sequence information of the present invention.

A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon a nucleotide sequence of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the nucleotide sequence information of the present invention on computer readable medium. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and Microsoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of data processor structuring formats (*e.g.* text file or database) in order to obtain computer readable medium having recorded thereon the nucleotide sequence information of the present invention.

By providing any of the nucleotide sequences SEQ ID NOs: 1 - 1104 or a representative fragment thereof; or a nucleotide sequence at least 95% identical to any

of the nucleotide sequences of the SEQ ID NOs: 1 - 1104 in computer readable form, a skilled artisan can routinely access the sequence information for a variety of purposes. Computer software is publicly available which allows a skilled artisan to access sequence information provided in a computer readable medium. The examples which follow demonstrate how software which implements the BLAST (Altschul et al., J. Mol. Biol. 215:403-410 (1990)) and BLAZE (Brutlag et al., Comp. Chem. 17:203-207 (1993)) search algorithms on a Sybase system is used to identify open reading frames (ORFs) within a nucleic acid sequence. Such ORFs may be protein encoding fragments and may be useful in producing commercially important proteins such as enzymes used in fermentation reactions and in the production of commercially useful metabolites.

As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the nucleotide sequence information of the present invention. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate that any one of the currently available computer-based systems are suitable for use in the present invention. As stated above, the computer-based systems of the present invention comprise a data storage means having stored therein a nucleotide sequence of the present invention and the necessary hardware means and software means for supporting and implementing a search means. As used herein, "data storage means" refers to memory which can store nucleotide sequence information of the present invention, or a memory access means which can access manufactures having recorded thereon the nucleotide sequence information of the present invention.

As used herein, "search means" refers to one or more programs which are implemented on the computer-based system to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of a known sequence which match a particular target sequence or target motif. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting

search means are and can be used in the computer-based systems of the present invention. Examples of such software includes, but is not limited to, Smith-Waterman, MacPattern (EMBL), BLASTN and BLASTA (NPOLYPEPTIDEIA). A skilled artisan can readily recognize that any one of the available algorithms or implementing software packages for conducting homology searches can be adapted for use in the present computer-based systems. As used herein, a "target sequence" can be any nucleic acid or amino acid sequence of six or more nucleotides or two or more amino acids. A skilled artisan can readily recognize that the longer a target sequence is, the less likely a target sequence will be present as a random occurrence in the database. The most preferred sequence length of a target sequence is from about 10 to 300 amino acids, more preferably from about 30 to 100 nucleotide residues. However, it is well recognized that searches for commercially important fragments, such as sequence fragments involved in gene expression and protein processing, may be of shorter length.

As used herein, "a target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration which is formed upon the folding of the target motif. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzyme active sites and signal sequences. Nucleic acid target motifs include, but are not limited to, promoter sequences, hairpin structures and inducible expression elements (protein binding sequences).

4.12 TRIPLE HELIX FORMATION

In addition, the fragments of the present invention, as broadly described, can be used to control gene expression through triple helix formation or antisense DNA or RNA, both of which methods are based on the binding of a polynucleotide sequence to DNA or RNA. Polynucleotides suitable for use in these methods are preferably 20 to 40 bases in length and are designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 15241:456 (1988); and Dervan et al., Science 251:1360 (1991))

or to the mRNA itself (antisense - Olmno, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide.

4.13 DIAGNOSTIC ASSAYS AND KITS

The present invention further provides methods to identify the presence or expression of one of the ORFs of the present invention, or homolog thereof, in a test sample, using a nucleic acid probe or antibodies of the present invention, optionally conjugated or otherwise associated with a suitable label.

In general, methods for detecting a polynucleotide of the invention can comprise contacting a sample with a compound that binds to and forms a complex with the polynucleotide for a period sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polynucleotide of the invention is detected in the sample. Such methods can also comprise contacting a sample under stringent hybridization conditions with nucleic acid primers that anneal to a polynucleotide of the invention under such conditions, and amplifying annealed polynucleotides, so that if a polynucleotide is amplified, a polynucleotide of the invention is detected in the sample.

In general, methods for detecting a polypeptide of the invention can comprise contacting a sample with a compound that binds to and forms a complex with the polypeptide for a period sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polypeptide of the invention is detected in the sample.

In detail, such methods comprise incubating a test sample with one or more of the antibodies or one or more of the nucleic acid probes of the present invention and assaying for binding of the nucleic acid probes or antibodies to components within the test sample.

Conditions for incubating a nucleic acid probe or antibody with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the nucleic acid probe or antibody used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification or immunological assay formats can readily be adapted to employ the nucleic acid probes or antibodies of the present invention. Examples of such assays can be found in Chard, T., An Introduction to Radioimmunoassay and Related Techniques, Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G.R. et al., Techniques in Immunocytochemistry, Academic Press, Orlando, FL Vol. 1 (1982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., Practice and Theory of immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1985). The test samples of the present invention include cells, protein or membrane extracts of cells, or biological fluids such as sputum, blood, serum, plasma, or urine. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing protein extracts or membrane extracts of cells are well known in the art and can be readily be adapted in order to obtain a sample which is compatible with the system utilized.

In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention. Specifically, the invention provides a compartment kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the probes or antibodies of the present invention; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound probe or antibody.

In detail, a compartment kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allows one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are

not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the antibodies used in the assay, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers which contain the reagents used to detect the bound antibody or probe. Types of detection reagents include labeled nucleic acid probes, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. One skilled in the art will readily recognize that the disclosed probes and antibodies of the present invention can be readily incorporated into one of the established kit formats which are well known in the art.

4.14 MEDICAL IMAGING

The novel polypeptides and binding partners of the invention are useful in medical imaging of sites expressing the molecules of the invention (e.g., where the polypeptide of the invention is involved in the immune response, for imaging sites of inflammation or infection). See, e.g., Kunkel et al., U.S. Pat. NO. 5,413,778. Such methods involve chemical attachment of a labeling or imaging agent, administration of the labeled polypeptide to a subject in a pharmaceutically acceptable carrier, and imaging the labeled polypeptide *in vivo* at the target site.

4.15 SCREENING ASSAYS

Using the isolated proteins and polynucleotides of the invention, the present invention further provides methods of obtaining and identifying agents which bind to a polypeptide encoded by an ORF corresponding to any of the nucleotide sequences set forth in the SEQ ID NOs: 1 - 1104, or bind to a specific domain of the polypeptide encoded by the nucleic acid. In detail, said method comprises the steps of:

(a) contacting an agent with an isolated protein encoded by an ORF of the present invention, or nucleic acid of the invention; and

(b) determining whether the agent binds to said protein or said nucleic acid.

In general, therefore, such methods for identifying compounds that bind to a polynucleotide of the invention can comprise contacting a compound with a polynucleotide of the invention for a time sufficient to form a polynucleotide/compound complex, and detecting the complex, so that if a polynucleotide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

Likewise, in general, therefore, such methods for identifying compounds that bind to a polypeptide of the invention can comprise contacting a compound with a polypeptide of the invention for a time sufficient to form a polypeptide/compound complex, and detecting the complex, so that if a polypeptide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

Methods for identifying compounds that bind to a polypeptide of the invention can also comprise contacting a compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a receptor gene sequence in the cell, and detecting the complex by detecting reporter gene sequence expression, so that if a polypeptide/compound complex is detected, a compound that binds a polypeptide of the invention is identified.

Compounds identified via such methods can include compounds which modulate the activity of a polypeptide of the invention (that is, increase or decrease its activity, relative to activity observed in the absence of the compound). Alternatively, compounds identified via such methods can include compounds which modulate the expression of a polynucleotide of the invention (that is, increase or decrease expression relative to expression levels observed in the absence of the compound). Compounds, such as compounds identified via the methods of the invention, can be tested using standard assays well known to those of skill in the art for their ability to modulate activity/expression.

The agents screened in the above assay can be, but are not limited to, peptides, carbohydrates, vitamin derivatives, or other pharmaceutical agents. The agents can be selected and screened at random or rationally selected or designed using protein modeling techniques.

For random screening, agents such as peptides, carbohydrates, pharmaceutical agents and the like are selected at random and are assayed for their ability to bind to the protein encoded by the ORF of the present invention. Alternatively, agents may be rationally selected or designed. As used herein, an agent is said to be "rationally selected or designed" when the agent is chosen based on the configuration of the particular protein. For example, one skilled in the art can readily adapt currently available procedures to generate peptides, pharmaceutical agents and the like, capable of binding to a specific peptide sequence, in order to generate rationally designed antipeptide peptides, for example see Hurby et al., Application of Synthetic Peptides: Antisense Peptides," In Synthetic Peptides, A User's Guide, W.H. Freeman, NY (1992), pp. 289-307, and Kaspczak et al., Biochemistry 28:9230-8 (1989), or pharmaceutical agents, or the like.

In addition to the foregoing, one class of agents of the present invention, as broadly described, can be used to control gene expression through binding to one of the ORFs or EMFs of the present invention. As described above, such agents can be randomly screened or rationally designed/selected. Targeting the ORF or EMF allows a skilled artisan to design sequence specific or element specific agents, modulating the expression of either a single ORF or multiple ORFs which rely on the same EMF for expression control. One class of DNA binding agents are agents which contain base residues which hybridize or form a triple helix formation by binding to DNA or RNA. Such agents can be based on the classic phosphodiester, ribonucleic acid backbone, or can be a variety of sulfhydryl or polymeric derivatives which have base attachment capacity.

Agents suitable for use in these methods preferably contain 20 to 40 bases and are designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while

antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide and other DNA binding agents.

Agents which bind to a protein encoded by one of the ORFs of the present invention can be used as a diagnostic agent. Agents which bind to a protein encoded by one of the ORFs of the present invention can be formulated using known techniques to generate a pharmaceutical composition.

4.16 USE OF NUCLEIC ACIDS AS PROBES

Another aspect of the subject invention is to provide for polypeptide-specific nucleic acid hybridization probes capable of hybridizing with naturally occurring nucleotide sequences. The hybridization probes of the subject invention may be derived from any of the nucleotide sequences SEQ ID NOs: 1 - 1104. Because the corresponding gene is only expressed in a limited number of tissues, a hybridization probe derived from of any of the nucleotide sequences SEQ ID NOs: 1 - 1104 can be used as an indicator of the presence of RNA of cell type of such a tissue in a sample.

Any suitable hybridization technique can be employed, such as, for example, in situ hybridization. PCR as described in US Patents Nos. 4,683,195 and 4,965,188 provides additional uses for oligonucleotides based upon the nucleotide sequences. Such probes used in PCR may be of recombinant origin, may be chemically synthesized, or a mixture of both. The probe will comprise a discrete nucleotide sequence for the detection of identical sequences or a degenerate pool of possible sequences for identification of closely related genomic sequences.

Other means for producing specific hybridization probes for nucleic acids include the cloning of nucleic acid sequences into vectors for the production of mRNA probes. Such vectors are known in the art and are commercially available and may be used to synthesize RNA probes *in vitro* by means of the addition of the appropriate RNA polymerase as T7 or SP6 RNA polymerase and the appropriate radioactively labeled nucleotides. The nucleotide sequences may be used to construct hybridization

probes for mapping their respective genomic sequences. The nucleotide sequence provided herein may be mapped to a chromosome or specific regions of a chromosome using well known genetic and/or chromosomal mapping techniques. These techniques include in situ hybridization, linkage analysis against known chromosomal markers, hybridization screening with libraries or flow-sorted chromosomal preparations specific to known chromosomes, and the like. The technique of fluorescent in situ hybridization of chromosome spreads has been described, among other places, in Verma et al (1988) Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York NY.

Fluorescent *in situ* hybridization of chromosomal preparations and other physical chromosome mapping techniques may be correlated with additional genetic map data. Examples of genetic map data can be found in the 1994 Genome Issue of Science (265:1981f). Correlation between the location of a nucleic acid on a physical chromosomal map and a specific disease (or predisposition to a specific disease) may help delimit the region of DNA associated with that genetic disease. The nucleotide sequences of the subject invention may be used to detect differences in gene sequences between normal, carrier or affected individuals.

4.17 PREPARATION OF SUPPORT BOUND OLIGONUCLEOTIDES

Oligonucleotides, i.e., small nucleic acid segments, may be readily prepared by, for example, directly synthesizing the oligonucleotide by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer.

Support bound oligonucleotides may be prepared by any of the methods known to those of skill in the art using any suitable support such as glass, polystyrene or Teflon. One strategy is to precisely spot oligonucleotides synthesized by standard synthesizers. Immobilization can be achieved using passive adsorption (Inouye & Hondo, (1990) J. Clin. Microbiol. 28(6) 1469-72); using UV light (Nagata *et al.*, 1985; Dahlen *et al.*, 1987; Morrissey & Collins, (1989) Mol. Cell Probes 3(2) 189-207) or by covalent binding of base modified DNA (Keller *et al.*, 1988; 1989); all references being specifically incorporated herein.

Another strategy that may be employed is the use of the strong biotin-streptavidin interaction as a linker. For example, Broude *et al.* (1994) Proc. Natl. Acad. Sci. USA 91(8) 3072-6, describe the use of biotinylated probes, although these are duplex probes, that are immobilized on streptavidin-coated magnetic beads. Streptavidin-coated beads may be purchased from Dynal, Oslo. Of course, this same linking chemistry is applicable to coating any surface with streptavidin. Biotinylated probes may be purchased from various sources, such as, e.g., Operon Technologies (Alameda, CA).

Nunc Laboratories (Naperville, IL) is also selling suitable material that could be used. Nunc Laboratories have developed a method by which DNA can be covalently bound to the microwell surface termed Covalink NH. CovaLink NH is a polystyrene surface grafted with secondary amino groups (>NH) that serve as bridge-heads for further covalent coupling. CovaLink Modules may be purchased from Nunc Laboratories. DNA molecules may be bound to CovaLink exclusively at the 5'-end by a phosphoramidate bond, allowing immobilization of more than 1 pmol of DNA (Rasmussen *et al.*, (1991) Anal. Biochem. 198(1) 138-42).

The use of CovaLink NH strips for covalent binding of DNA molecules at the 5'-end has been described (Rasmussen et al., (1991). In this technology, a phosphoramidate bond is employed (Chu et al., (1983) Nucleic Acids Res. 11(8) 6513-29). This is beneficial as immobilization using only a single covalent bond is preferred. The phosphoramidate bond joins the DNA to the CovaLink NH secondary amino groups that are positioned at the end of spacer arms covalently grafted onto the polystyrene surface through a 2 nm long spacer arm. To link an oligonucleotide to CovaLink NH via an phosphoramidate bond, the oligonucleotide terminus must have a 5'-end phosphate group. It is, perhaps, even possible for biotin to be covalently bound to CovaLink and then streptavidin used to bind the probes.

More specifically, the linkage method includes dissolving DNA in water (7.5 ng/ul) and denaturing for 10 min. at 95°C and cooling on ice for 10 min. Ice-cold 0.1 M 1-methylimidazole, pH 7.0 (1-MeIm$_7$), is then added to a final concentration of 10 mM 1-MeIm$_7$. A ss DNA solution is then dispensed into CovaLink NH strips (75 ul/well) standing on ice.

Carbodiimide 0.2 M 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), dissolved in 10 mM 1-MeIm$_7$, is made fresh and 25 ul added per well. The strips are incubated for 5 hours at 50°C. After incubation the strips are washed using, e.g., Nunc-Immuno Wash; first the wells are washed 3 times, then they are soaked with washing solution for 5 min., and finally they are washed 3 times (where in the washing solution is 0.4 N NaOH, 0.25% SDS heated to 50°C).

It is contemplated that a further suitable method for use with the present invention is that described in PCT Patent Application WO 90/03382 (Southern & Maskos), incorporated herein by reference. This method of preparing an oligonucleotide bound to a support involves attaching a nucleoside 3'-reagent through the phosphate group by a covalent phosphodiester link to aliphatic hydroxyl groups carried by the support. The oligonucleotide is then synthesized on the supported nucleoside and protecting groups removed from the synthetic oligonucleotide chain under standard conditions that do not cleave the oligonucleotide from the support. Suitable reagents include nucleoside phosphoramidite and nucleoside hydrogen phosphorate.

An on-chip strategy for the preparation of DNA probe for the preparation of DNA probe arrays may be employed. For example, addressable laser-activated photodeprotection may be employed in the chemical synthesis of oligonucleotides directly on a glass surface, as described by Fodor *et al.* (1991) Science 251(4995) 767-73, incorporated herein by reference. Probes may also be immobilized on nylon supports as described by Van Ness *et al.* (1991) Nucleic Acids Res. 19(12) 3345-50; or linked to Teflon using the method of Duncan & Cavalier (1988) Anal. Biochem. 169(1) 104-8; all references being specifically incorporated herein.

To link an oligonucleotide to a nylon support, as described by Van Ness *et al.* (1991), requires activation of the nylon surface via alkylation and selective activation of the 5'-amine of oligonucleotides with cyanuric chloride.

One particular way to prepare support bound oligonucleotides is to utilize the light-generated synthesis described by Pease *et al.*, (1994) PNAS USA 91(11) 5022-6, incorporated herein by reference). These authors used current photolithographic techniques to generate arrays of immobilized oligonucleotide probes (DNA chips). These

methods, in which light is used to direct the synthesis of oligonucleotide probes in high-density, miniaturized arrays, utilize photolabile 5'-protected *N*-acyl-deoxynucleoside phosphoramidites, surface linker chemistry and versatile combinatorial synthesis strategies. A matrix of 256 spatially defined oligonucleotide probes may be generated in this manner.

4.18 PREPARATION OF NUCLEIC ACID FRAGMENTS

The nucleic acids may be obtained from any appropriate source, such as cDNAs, genomic DNA, chromosomal DNA, microdissected chromosome bands, cosmid or YAC inserts, and RNA, including mRNA without any amplification steps. For example, Sambrook *et al.* (1989) describes three protocols for the isolation of high molecular weight DNA from mammalian cells (p. 9.14-9.23).

DNA fragments may be prepared as clones in M13, plasmid or lambda vectors and/or prepared directly from genomic DNA or cDNA by PCR or other amplification methods. Samples may be prepared or dispensed in multiwell plates. About 100-1000 ng of DNA samples may be prepared in 2-500 ml of final volume.

The nucleic acids would then be fragmented by any of the methods known to those of skill in the art including, for example, using restriction enzymes as described at 9.24-9.28 of Sambrook *et al.* (1989), shearing by ultrasound and NaOH treatment.

Low pressure shearing is also appropriate, as described by Schriefer *et al.* (1990) Nucleic Acids Res. 18(24) 7455-6, incorporated herein by reference). In this method, DNA samples are passed through a small French pressure cell at a variety of low to intermediate pressures. A lever device allows controlled application of low to intermediate pressures to the cell. The results of these studies indicate that low-pressure shearing is a useful alternative to sonic and enzymatic DNA fragmentation methods.

One particularly suitable way for fragmenting DNA is contemplated to be that using the two base recognition endonuclease, *Cvi*JI, described by Fitzgerald *et al.* (1992) Nucleic Acids Res. 20(14) 3753-62. These authors described an approach for the rapid fragmentation and fractionation of DNA into particular sizes that they contemplated to be suitable for shotgun cloning and sequencing.

The restriction endonuclease *Cvi*JI normally cleaves the recognition sequence PuGCPy between the G and C to leave blunt ends. Atypical reaction conditions, which alter the specificity of this enzyme (*Cvi*JI**), yield a quasi-random distribution of DNA fragments form the small molecule pUC19 (2688 base pairs). Fitzgerald *et al.* (1992) quantitatively evaluated the randomness of this fragmentation strategy, using a *Cvi*JI** digest of pUC19 that was size fractionated by a rapid gel filtration method and directly ligated, without end repair, to a lac Z minus M13 cloning vector. Sequence analysis of 76 clones showed that *Cvi*JI** restricts pyGCPy and PuGCPu, in addition to PuGCPy sites, and that new sequence data is accumulated at a rate consistent with random fragmentation.

As reported in the literature, advantages of this approach compared to sonication and agarose gel fractionation include: smaller amounts of DNA are required (0.2-0.5 ug instead of 2-5 ug); and fewer steps are involved (no preligation, end repair, chemical extraction, or agarose gel electrophoresis and elution are needed

Irrespective of the manner in which the nucleic acid fragments are obtained or prepared, it is important to denature the DNA to give single stranded pieces available for hybridization. This is achieved by incubating the DNA solution for 2-5 minutes at 80-90°C. The solution is then cooled quickly to 2°C to prevent renaturation of the DNA fragments before they are contacted with the chip. Phosphate groups must also be removed from genomic DNA by methods known in the art.

4.19 PREPARATION OF DNA ARRAYS

Arrays may be prepared by spotting DNA samples on a support such as a nylon membrane. Spotting may be performed by using arrays of metal pins (the positions of which correspond to an array of wells in a microtiter plate) to repeated by transfer of about 20 nl of a DNA solution to a nylon membrane. By offset printing, a density of dots higher than the density of the wells is achieved. One to 25 dots may be accommodated in 1 mm^2, depending on the type of label used. By avoiding spotting in some preselected number of rows and columns, separate subsets (subarrays) may be formed. Samples in one subarray may be the same genomic segment of DNA (or the same gene) from different individuals, or may be different, overlapped genomic clones. Each of the subarrays may

represent replica spotting of the same samples. In one example, a selected gene segment may be amplified from 64 patients. For each patient, the amplified gene segment may be in one 96-well plate (all 96 wells containing the same sample). A plate for each of the 64 patients is prepared. By using a 96-pin device, all samples may be spotted on one 8 x 12 cm membrane. Subarrays may contain 64 samples, one from each patient. Where the 96 subarrays are identical, the dot span may be 1 mm^2 and there may be a 1 mm space between subarrays.

Another approach is to use membranes or plates (available from NUNC, Naperville, Illinois) which may be partitioned by physical spacers e.g. a plastic grid molded over the membrane, the grid being similar to the sort of membrane applied to the bottom of multiwell plates, or hydrophobic strips. A fixed physical spacer is not preferred for imaging by exposure to flat phosphor-storage screens or x-ray films.

The present invention is illustrated in the following examples. Upon consideration of the present disclosure, one of skill in the art will appreciate that many other embodiments and variations may be made in the scope of the present invention. Accordingly, it is intended that the broader aspects of the present invention not be limited to the disclosure of the following examples. The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention, and compositions and methods which are functionally equivalent are within the scope of the invention. Indeed, numerous modifications and variations in the practice of the invention are expected to occur to those skilled in the art upon consideration of the present preferred embodiments. Consequently, the only limitations which should be placed upon the scope of the invention are those which appear in the appended claims.

All references cited within the body of the instant specification are hereby incorporated by reference in their entirety.

5.0 EXAMPLES

5.1 EXAMPLE 1

Novel Nucleic Acid Sequences Obtained From Various Libraries

A plurality of novel nucleic acids were obtained from cDNA libraries prepared from various human tissues and in some cases isolated from a genomic library derived from human chromosome using standard PCR, SBH sequence signature analysis and Sanger sequencing techniques. The inserts of the library were amplified with PCR using primers specific for the vector sequences which flank the inserts. Clones from cDNA libraries were spotted on nylon membrane filters and screened with oligonucleotide probes (e.g., 7-mers) to obtain signature sequences. The clones were clustered into groups of similar or identical sequences. Representative clones were selected for sequencing.

In some cases, the 5' sequence of the amplified inserts was then deduced using a typical Sanger sequencing protocol. PCR products were purified and subjected to fluorescent dye terminator cycle sequencing. Single pass gel sequencing was done using a 377 Applied Biosystems (ABI) sequencer to obtain the novel nucleic acid sequences. In some cases RACE (Random Amplification of cDNA Ends) was performed to further extend the sequence in the 5' direction.

5.2 EXAMPLE 2

Novel Nucleic Acids

The novel nucleic acids of the present invention of the invention were assembled from sequences that were obtained from a cDNA library by methods described in Example 1 above, and in some cases sequences obtained from one or more public databases. The nucleic acids were assembled using an EST sequence as a seed. Then a recursive algorithm was used to extend the seed EST into an extended assemblage, by pulling additional sequences from different databases (i.e., Hyseq's database containing EST sequences, dbEST version 114, gb pri 114, and UniGene version 101) that belong to this assemblage. The algorithm terminated when there was no additional sequences from the above databases that would extend the assemblage. Inclusion of component sequences into the assemblage was based on a BLASTN hit to the extending assemblage with BLAST score greater than 300 and percent identity greater than 95%.

Using PHRAP (Univ. of Washington) or CAP4 (Paracel), a full length gene cDNA sequence and its corresponding protein sequence were generated from the

assemblage. Any frame shifts and incorrect stop codons were corrected by hand editing. During editing, the sequence was checked using FASTY and/or BLAST against Genbank (i.e., dbEST version 117, gb pri 117, UniGene version 117, Genepet release 117). Other computer programs which may have been used in the editing process were phredPhrap and Consed (University of Washington) and ed-ready, ed-ext and gc-zip-2 (Hyseq, Inc.). The full-length nucleotide and amino acid sequences, including splice variants resulting from these procedures are shown in the Sequence Listing as SEQ ID NOS:1- 1104.

Table 1 shows the various tissue sources of SEQ ID NO: 1-1104.

The nearest neighbor results for SEQ ID NO: 1-1104 were obtained by a BLASTP version 2.0al 19MP-WashU search against Genpept release 118, using BLAST algorithm. The nearest neighbor result showed the closest homologue for SEQ ID NO: 1-1104 from Genpept (and contains the translated amino acid sequences for which the nucleic acid sequence encodes). The nearest neighbor results for SEQ ID NO: 1-1104 are shown in Table 2 below.

TABLE 1

TISSUE ORIGIN	RNA SOURCE	HYSEQ LIBRARY NAME	SEQ ID NOS:
adult brain	GIBCO	AB3001	4-5 7 29-30 35 42 52 55-56 90 97 117 133-134 147 149 151 162 170 174 177 193 201 222 250 258 263 285-286 290 295 311-312 323-324 330 336-337 339 348 351-353 360 369 377 379 392 398 408 415 459-461 480 489 496 542-544 547 554 584-585 597 599 606 609 611-616 620 623 649 666 675-676 683 688 691-693 695-696 706 727 735 748 753 756 759 767 771 796 802 805-806 820 823-826 829 838 840 846 869 895 919 924 931 933 948 962-963 969 978-980 984 997-998 1002 1010 1013 1020 1046 1050-1051 1058 1063-1065 1069 1081 1090
adult brain	GIBCO	ABD003	2-4 6-7 18-22 29-30 52-54 66 74 82 88 93 98 100-102 104 107-110 112-113 117 119 123 127-128 133-135 142 145-147 150-152 157 165 168 170 174 177 181-182 190 193-195 200-202 209 211-215 217-218 220 228 230 236 245-246 250-252 262-264 269 272 274 278 283-286 293-297 299-300 302 305-311 313-314 321 323-327 331 333-335 339-340 343-346 348 350-352 358 363 369 383 392-393 398 401 408-412 419 427 429-430 434 437 443 449-450 457 459-462 470 473 480 484-485 487-488 495-496 500 502 505-506 517 519-521 525 530-532 536 543-546 549 554 559 563 568 582 586-587 589-590 593 596 598-601 603 608-609 611-614 616 619-621 623-626 628-629 632 642-645 650 653-656 664 666-667 672-673 677 679-680 684-688 692-693 695 700 705-708 711-712 717-719 722 724 727 738 748 752-755 767 770-771 774-775 778 786 792 796 798 801 805-806 808 810 813 816 819 823 833-834 838 840 846-847 856 859 867 873 877 879 882-883 889 891 904-906 909 915-916 919 921 931 933 937 942 948 953 957 959 969 971 974 976-979 983-984 996-997 1002 1006-1010 1016 1023 1028 1031 1034 1038 1041 1045-1047 1058 1064 1067 1070 1076 1079-1080 1084 1090 1100
adult brain	Clontech	ABR001	3-4 17 21 25 35 52 57 66 78 82

TABLE 1

			88 115-116 128 143 155 164 180 191 262 274 309 319 338 373 398 484 488 518 550 556 560 565 567 593 607 624 687 692-694 715 724 729 731 764 796 801 810 816 825-826 833-836 921 928-929 970 983 1010 1035 1045 1051 1073-1074 1090
adult brain	Clontech	ABR006	9-11 14 25 30 32-33 35 42 47 52 57 66 69-70 88 93-94 100-102 104 115-116 127 180 293-294 340 371 469 483 530 598 706 742 798 802 813 837 856 876 896 916 952 955 975 1002 1007-1009 1014-1017 1034 1059 1071 1090
adult brain	Clontech	ABR008	1 3-4 6-11 14 17-20 22 25 27 29-30 35 42-46 49 52-53 55 57 60 63-64 66-67 70 72-76 79-85 88-89 91-94 100-102 111-112 114-118 127-129 136 138 141 143-145 150 152 156-158 162-165 171 177 180-187 190-191 194-195 199-201 203-205 207-209 212-215 217 219 222-226 228 237 241-243 248-250 253 257 261 263-264 266-267 271 274 276 278-279 283-287 289 292-294 296-297 299-300 305-307 309 311-312 314-319 321 323-325 329-331 334-340 343-345 348 351-353 355 361 364 369 371 373-382 384 388 392-393 398-401 404-405 409-418 420-423 426-427 430 434-436 440 442-443 446-448 450 452 457-462 464-466 468-469 471-473 478 480 484 487-488 490 496 499-500 503 510-511 519-522 524-525 527-528 541-544 546-547 550 552-557 559-560 566 568-569 572 574-577 579-580 582-583 586 589 593 595 597-599 601 604 606 608-611 613-614 617-619 622-628 630 632 636 640-641 645 648-650 654 656 658 662 664 668-670 673 675-677 679 684 686-689 691-693 696 700 706-711 715 717-719 723-725 735-736 741 746 748 752 757 759 761-764 766 770-772 774-782 784-785 797-801 803-814 816 820-822 824-827 831-834 837-847 849-852 856 858 861 864 866 869 872-877 880-884 888-889 893 895 900 902-905 911-912 915-916 919-921 924-925 931-932 934-953 956 959-961 966-967 969-971 974-976 982 984-985 989 995-999 1002 1004 1006-1009 1012 1014-

TABLE 1

			1017 1020 1022 1024-1025 1029 1034-1036 1041 1044-1045 1047-1048 1055-1057 1059-1060 1063-1064 1066-1069 1071-1074 1076-1078 1082 1084 1086-1087 1090 1094-1098 1101
adult brain	Clontech	ABR011	37-38 182 300 392 624 689-690 748 893
adult brain	BioChain	ABR012	423 451 1061
adult brain	BioChain	ABR013	37-38 66 171 272 369 374-376 515 530 757 1010 1104
adult brain	Invitrogen	ABR014	30 37-38 48 128 137 415 544 626 670 762 952 960 1010 1094
adult brain	Invitrogen	ABR015	93 108-109 115-116 447 473 670 1010
adult brain	Invitrogen	ABR016	37-38 52 1010 1024-1025
adult brain	Invitrogen	ABT004	9-11 19-20 22-23 29-30 35 44 52-53 55-56 64 66 69 72 74 82 102 112 133 135 150 156 164 176 181-183 190 201 206 233 238 274 279 284-286 301 330 334 349 351 353-354 369-371 377-378 392 395 398 405 416 423 427 434 437 450 462 464-465 473 488 499 511 515 522 526 542 554 559 579-580 612 624 636 641-643 647-648 650 655-656 675-676 687 692-693 704-707 709 724-725 740 742 775 779 798 802 804 809-810 812-813 825-826 829 833-836 840 856 859 863 877 882-883 894 914 919 921 944 948 952 970 975 999 1002 1024-1025 1031 1033-1034 1046-1047 1060 1068-1069 1073-1074 1094-1095
adipocytes	Strategene	ADP001	4 9-11 52-53 64 73 102 104-105 184-186 194 199 202 224 233 237 279 295 297 299 309 315 325 352 363-364 392 415 432 466 477-478 502 519-521 528 530 543-544 564 567 578-580 621 647 669 673 682-683 687 689 692-693 695 713 715-716 720 727 733 760 767 786 788-791 825-826 829 908-909 918 950 961 987-988 1004 1010 1012 1019 1029 1035 1055-1056 1060-1061 1088 1099
adrenal gland	Clontech	ADR002	9-11 15 22 24-25 27 45-46 56-58 64 73 84 89-90 98 100-101 105 108-111 113 119 128 135 147 151 157 165 167 171-172 177 190 193 202 210 221 224 227 248-249 257 264 272 277 279 285-287 297 305-306 308 315 323-324 348 352 361 385 393 396 398 403 416 418 428-430 442 457-462 473 501 514

TABLE 1

			522 530 533 554 560 568 583 589 599 609-610 617-618 629 635 639 652 654 656 663-664 668 677 679-680 688 691 694 737 742 744 748 760-761 765 801-802 804 810 816 823-824 840 847 852 864 870 877 898 907 913-914 916 921 933 960-961 964 970 975 980 983 997 1014-1015 1017 1020 1032-1033 1035 1038 1055-1056 1059 1068-1069 1077 1088 1090 1096
adult heart	GIBCO	AHR001	3 6 9-11 18 22 24-25 27 31 34 41 43 53 56-57 60-61 64 66 70 74 80 82-83 85-86 88-90 104-105 107-113 119-120 123 126 128-129 131 133 136 143 146-147 150-154 157-158 161-164 166-167 170-172 177 180 182 184-187 190 193-194 196-197 201 209 211-215 217 221 224 228 231 236-238 250-253 257-258 260 262-263 265 269 272 274 281-286 288-289 292-297 299-300 303 310 315 323-330 333 335-339 341-342 346-347 352-354 356-357 365-366 369 374-376 379 383 391 393 395 398-400 403-404 409-410 412 414-416 419 422-423 427-428 430 435 437 443 445 449 454-455 459-464 469 472-474 480 487 489 495 497 502 506 511 513 515 522 528 530-532 534-538 542-546 548-549 554 556 560 562-564 566 568 572 575-577 579-580 582-583 586 588 591-592 596-597 599-600 602 606 608-612 614-615 620-622 632 645 648-650 654 656-659 662 664-665 667-673 677 679 686-689 692-695 698 704 707-708 710-711 713 716-725 727-728 731 735 738 743-744 746 748 752-753 756-757 759 761 764-765 772 774-776 778 782-783 793 795 797-798 802 805-806 808 810 813 815 817 820-823 833-834 837-838 840 847 856 858-859 864 866 881 885 888-889 891 895-897 900 905 907 911 916-919 922-925 928-931 933-934 937-938 940 943-944 946-948 951 958 960-961 967 970-972 977 982 988-989 996 998 1007-1011 1014-1015 1020 1022 1024-1027 1029 1034-1035 1039-1040 1044-1046 1049-1050 1055-1056 1059 1061 1064-1065 1068-1070 1073-1074 1079 1087 1090 1094 1100
adult kidney	GIBCO	AKD001	2-4 6 14 17 21-23 25 29 31-32

TABLE 1

			35 37-38 41 43-45 47 49-50 53-55 65 68 71 73-74 78 81-83 88-89 97-98 104-111 117-118 120 123 125 127-129 133 135-136 138 141 143 145-148 150-151 154-155 157 161-162 164-165 167 171-179 184-187 190-194 197 199 201-204 209 212-215 219 222 224 229-230 232 236 238 240 243 247-252 254 258 262-265 268-269 275-276 278 281-283 285-290 292-296 298-303 310-312 315-321 323-330 333-334 339-340 343-345 351-354 358 360-361 370 374-377 380 384 393-394 396 400-401 403-404 411 415 419-420 422 427 429-430 435 437 439 446-447 449 455-457 459-462 464 470 472 477 479-481 485 488 490 493 495-497 499-504 506 511 514 517 519-523 527-530 533-540 542-546 549-550 552 554 556 559 561-568 571-572 574-576 578-581 583-585 587 591-593 595-597 599-601 605 607 609 612-614 616-622 624 627-629 632 635-636 638 640-645 647-648 650-651 656-657 659 663-665 669-673 675-677 679-680 682-684 686-689 691-696 698 700-701 704-705 707-708 710 713-719 723 726-728 730 732 735 738 742-744 746-753 757 759-762 767 774-775 777-778 781 783 786 788-791 796 798-801 805-808 810 812-814 821-824 829 831-832 835-836 838-839 842-843 846 848 852 856 859 867-868 870 872 881 885-889 891-893 895-900 905-908 910-911 914 916-917 919-920 922-924 928-931 933-934 936-937 943 947-948 950-951 957-958 960 962-964 971 973 977-979 983-985 989 996 998 1001-1003 1007-1010 1013 1019-1020 1024-1025 1029 1031 1039-1040 1043-1047 1049 1057 1059 1063 1065 1068-1069 1084 1087 1090 1094 1096 1098-1100
adult kidney	Invitrogen	AKT002	12 14 17-18 22 31 43-45 49 55-56 60 65 74 88 90 95 104 117 119 123 127-128 146 161-162 178 180 187 190 193 197 203 211-215 221 229 261 263 270 275 279 284 293-294 303-304 307 314 321 333 343-345 377 391 405 419 427 445 452 459-461 472 480 489 499 512 522-523 534-535 537-538 554-555

TABLE 1

			566 575-577 583 588 590-592 601 606 612 614 621 628 636 639 644 647 649 655 657 687 696 717-718 732 740 744 752 756-757 762 774 788-791 796 799-800 802 804 808 815 823 825-826 835-837 842 848 881 885 888 922-923 931 946 954 962-963 971 975 983-984 989 1002 1010 1014-1015 1020 1034 1039 1041 1045-1046 1059 1068-1069 1094
adult lung	GIBCO	ALG001	5 18 24 35 44 54-55 67 82-83 105 110 119 128 133 135 141 143 145 150-151 162 178 187 202 212-215 219 222-223 229 240 259 284 293-294 298 300-301 312 323-324 333 343-345 352 377 393 399 403 427-428 447 450 458 473 488 496 499 502 516-517 522-523 530 537-538 543-544 546 551 565 572 586 590 628 641-644 653 658 664 666 668 674 677 679 683 688 692-693 702 705 733 735 743 748 751 753 761 769 775-778 783 796 815 823 825-826 831 839 846 862 879 889 897 909 931 962-963 970 972 985 996 1010 1021-1022 1043 1064 1069 1073-1074 1095 1100
lymph node	Clontech	ALN001	2 16 55 77 95 104 107 119 125 135-136 149 155-156 177 201 204 212-215 221-222 298 303 327 333 361 403 409-410 422 477 481 488 516 519-521 523 529 542-543 551 564 590 600 615 650 663 692-693 700 726 738 805-806 840 888 893 915 933 955 964 1014-1015 1029 1043 1064 1067
young liver	GIBCO	ALV001	15 24 29 32 35 45 47 65 67 71 74 81-82 84 88 105 118 129 133 150 152 157 167 184-186 190 194 197 201 211 224 247 250-253 261 268 278-279 284 298-301 305-306 308 310-311 315 326 339 347 349 360 379-380 382 401 403 412 414 418 422 428-429 450 454 457 463 472 485 493 497 499 526 534-536 556 559 564 572 578 583-585 587-589 591-592 596-597 606 609 611 621 640 644 650 652 657 671 673 684 688 691 695 700 717-718 721-722 740 750 755 759 765 775 778 782 788-791 799-801 805-806 808 810 814 825-826 833-834 845-846 848 885 888-889 898 900 908-909 931 934 952 960 965 969 973 985 1007-1010 1022 1029

TABLE 1

			1034 1049 1052-1053 1069 1073-1074 1094
adult liver	Invitrogen	ALV002	6 29 32 47 49 71 74 82 88 102 104 107-109 128 150 168 177-179 191-192 203 209 219 227 237-239 243 254 257 285-286 308 310 315 322 328 333 340 346 354 384 389 392 405-406 434 437 462 466 478 499 505 511 519-522 532 534-535 543 546 559 564 578 583 589 596 605 608-609 613 633 635 659 665 673 683 694 708 715 719 722 741 752 757 759 762 775 778 782 786 802 808 845 848 884 887-888 897 909 916 931 951 962-963 967 975 998 1005 1010 1014-1015 1020 1052-1053 1065 1094 1099-1100
adult liver	Clontech	ALV003	358 684 752 808
adult ovary	Invitrogen	AOV001	3 5-6 8-11 14 17 22 25-26 29 31 33 35 43-45 49-50 52-57 60 63-65 67 70-71 73 76 82-84 86 88-90 97-98 100-101 104-109 113 117-120 122-123 125 127-129 136-137 142-145 147 150-153 155-158 161 163-168 170-171 173-175 177-179 183-188 190-191 193-195 197 199 201 203-209 216-219 221-222 224 227 229-231 237-240 242-243 245-246 248-249 251-252 255 257 259 261-264 266-267 269 272 274 276 278-282 284-290 292 295-299 301-304 307-308 310-311 314-318 320 322-325 327-330 332-334 336-346 348-357 359-360 363 365-366 374-377 379-393 397-405 407 409-411 413 416 418-419 427-430 434-435 437 442 447 449 451 456-457 459-462 464 467-468 470 472 474-475 478-480 485 488 490 494-496 498-500 503-504 506-509 511 513-514 516-517 522-523 528-535 537-542 544-549 552 554 556-557 559-560 563-568 572-573 575-580 583-595 597-601 603 606-609 611 613-614 616-626 628 630-633 635-638 640 642-645 648-651 653-654 657-666 668-669 672-673 675-677 679 682-684 686-688 691-697 699-701 704 707-708 712-713 717-719 721-723 725 727 729-735 738-739 742-749 751-753 756-759 761-762 764-765 767-768 774-775 778-779 783-785 787-792 795-797 801-806 808-809 812-816 820-824 831-832 835-838

TABLE 1

			842 845 847 852 854-855 858-860 862-864 866-867 869 872-874 879-880 884 886-889 891 894-903 906-908 910-915 922-925 928-931 933-934 937 939 942-944 946-948 952 955 957-958 960 965 968 970-973 976-979 981 983-984 988-989 996 998 1002 1007-1011 1013 1017 1019-1020 1022-1023 1028-1029 1031 1033-1041 1046 1049 1051 1055-1056 1061-1065 1067-1069 1073-1074 1076 1079 1084 1090 1095
adult placenta	Clontech	APL001	24 88 150 177 220 250 301 314 403 439 457 545 575-576 611 634 642-643 649 677 679 689 733 742 891 1010 1059
adult placenta	Invitrogen	APL002	2 7 12 32 52-53 91 97 104 108-109 122 128 157 164-165 191 197 309 407 409-410 412 422 430 453 503 528 539-540 542-543 603 635 640-641 663 675-676 692-693 701 721 724 753 757 759 775 828 833-834 849 967 975 1007-1010 1033 1035
adult spleen	GIBCO	ASP001	6 14 22 31 45 55 59-60 67 77 80 88 105 108-110 120 122 125 147 155 164-167 174 177 179 191 193 205 209 211-215 222 229 233 250-252 258 268 272 281 288-289 297-298 300 309-310 320 330 333 338 340 349 353 355-357 366 382 393 405 412 414 416 422 426-428 430 446 449 458 464 472-473 478 495-496 502 507 515 517 530 533 537-538 543 547 551 559 564 567 569 591-593 599 606 608-610 613-614 621 629 636 644-645 650 664-665 670 677 679-681 683-684 686 692-693 695 698 700 719 724 730-732 734 737 748 757 759 765 778-779 783 792 798 802 804 813 829 852 859 863 866 879 885 908-909 915-916 919 926 931 936 948 959 961 964 985 991 1010 1012 1020 1024-1025 1029 1039 1041 1043 1049-1050 1054 1059 1064 1076 1087 1104
adult testis	GIBCO	ATS001	3 7 22 43-45 65 71 84 89 100-101 104-105 107 111 120 128 135 143 147 151 155-156 167 173 176-177 187 197 201 222 227-228 239-240 248-249 251-252 257-258 261 276-279 282 289 292-294 297 307 309 315 325 327-328 333 335 339 346 352 356-357 395 403-405

TABLE 1

			407 412 415 422 428 430 457 464 468 472-473 487 489 494 496 499 511 516 522 528 530 533 544 551 554 562 590 597 600 603 606 608 613 616 624 637 647 650 658 662 664 668 677 679-680 695 704 717-718 722-723 726-727 733 748-749 753 759 761-762 776 778 786 788-791 793 797 802 830 838 850-851 864 897-898 911 916 919 921 925 928-929 933 943 975 977-979 981-983 997 1001 1007-1010 1020 1022 1028 1035 1059 1063-1064 1069 1079 1089-1090 1100
Genomic DNA from BAC 63I18	Research Genetics (CITB BAC Library)	BAC001	368 1042 1103
Genomic DNA from BAC 393I6	Research Genetics (CITB BAC Library)	BAC002	1102-1103
Genomic DNA from BAC 393I6	Research Genetics (CITB BAC Library)	BAC003	1042
adult bladder	Invitrogen	BLD001	21 36 55 87 89 98 104 117 157 176 217-218 238 240 284 293-294 303 313 330 349 353 392 411 439-440 446 457 470 472 522 525 551 578 583 594 605 616 653 664 670 704 713 744 762 771 829 856 874 878 888 960 1059
bone marrow	Clontech	BMD001	3 6 12 16 25 30-31 43-44 55 57-58 60 62 67 77 82 84 86 90 95 98-101 103-105 110-111 113 115-116 119 121 128-130 135-136 145-146 149 151-153 155-156 159 162 167 172 174 177-180 187 190 193 198-199 201 205 210-215 217 219-220 224 230-231 241 243 245-253 257 259-262 264 269 271 278 280-281 285-286 290-296 298-299 307 310-311 314-315 320 327-328 333 335-339 347 352 354 356-357 361 365 383 390 393 399-400 402-404 415 419-420 424-426 428-429 436 445 449 456-457 459-462 464 469-470 473-475 480 483 487 495-497 508-509 511 515 517-518 522-523 528-529 533-540 543-544 551-552 554 563-565 568 575-577 581 588 590 593 598-601 609-611 614 617-618 624 626-628 639-640

TABLE 1

			642-645 650 656 660 663 668 672 674 677 679 682 687 689 692-693 695 701 704 713 716-719 721 723 725 727 730 732 735 738 741-743 748 750 752 755 759-760 768 795 799-802 804-806 813 815 823-824 831 833-834 852 861 867 886 888-889 891 905-906 913 916-918 930 936 944 951 956 960 968 971 975 977 980-981 983 989-991 998 1004 1007-1010 1017 1021 1029 1033 1036 1039 1043 1046 1051 1057 1059 1062-1064 1069-1070 1084 1090 1093-1094 1097 1099 1104
bone marrow	Clontech	BMD002	3 7-8 21 25-26 30 33 43-46 57 59-60 70 76-78 88-90 95 99-101 103-104 107-110 114 118 125 128 139-140 146 149 152 165 167 190 194 198 200 206 220 223 227 242 245-246 257 259 266-267 271 274-275 278 293-294 298 319 328 330 335 338 353 356-357 361 366 392 402-403 412 418 421-422 426 445 449 458-462 474 496 499 503 515 519-521 539-540 544 551 554 556 563-564 569 574 577 589 609-610 619 677 679 685 688 691 704 724 730 736 739 743-744 747 777-778 795 801-803 844 846 881 889 912 916-917 926-927 950-951 972-973 975 977 985 1004 1007-1011 1014-1017 1020 1023 1031 1033 1037 1040 1043 1045-1047 1057 1059-1060 1063 1067 1069 1071 1073-1074 1084 1087 1090 1097 1104
bone marrow	Clontech	BMD004	177 609 724
bone marrow	Clontech	BMD007	551 1010
adult colon	Invitrogen	CLN001	6 32 59 61 67 82 94 129 155 159 177 184-186 266-267 292 313 325-326 346 354 366 379 392 409-410 427 464 470 472 511-512 533-535 539-540 543 551 557 583 605 608-610 640 663 670 680 692-693 705 708 713 715 743-744 752 757-758 829 842 859 874 885 888 909 970 1004-1005 1010 1035 1041 1045 1059
Mixture of 16 tissues-mRNAs*	Various Vendors*	CTL016	74

TABLE 1

Mixture of 16 tissues- mRNAs*	Various Vendors*	CTL021	466 821-822 1094
adult cervix	BioChain	CVX001	2-3 5 8 15 25 31 35 44-45 49 52 54-55 57 61 71 73 84 88 90 93-94 100-101 104-105 107-110 113 120 122 135-136 138 145-151 153 156-157 165 167 170 177 180 184-187 190-191 201 205 210 217-219 221-222 233 237 248-249 251-253 257-258 261-262 264-265 269-270 277 279 281-282 284-286 289 292-296 300 322 328 332-333 336-337 343-346 352 354 362 365 373-376 380 388 390-391 393-394 396 404-405 411 413 415-416 421 429-431 437-438 444 449 455 458-461 464 474 477 480-481 483 485 488 490 503 511 513 516-517 519-521 528 532-533 536-540 542-545 549-551 554 556 561 563-565 567 572 575-576 582 584-587 590-593 598-600 603 605-606 609 614 619 621-625 631 635 642-643 645 650-651 654 656-657 659 663 665-666 670 672 677 679 687 692-695 704-705 712 715 721 724 726 733 735 741 743-745 755-756 760 762 764 768 771 787 802 813 818 823 828 835-838 852 856 859 862 864 866 870 886 889 891 900 903 905 910-911 914 916 922-924 930-931 933 948 954-955 958 960 969 977-980 998 1000-1001 1006 1010 1013 1017 1035 1039 1043-1044 1050 1062-1064 1073-1074 1076 1084 1087 1096-1097
diaphragm	BioChain	DIA002	414 464 673 1100
endothelial cells	Strategene	EDT001	2 4-6 8 13 15 24-28 33 44 48 53-55 57 60 63 65 70 73 81-82 84 86 88 90 99-101 105 108-110 113 118-119 123 128 137-138 146-149 151-153 160 162-164 171-172 174-178 184-187 190-193 197 199 201-203 207-209 211-215 217-221 223 237-239 242-243 248-252 255 257 261-262 265 269

* The 16 tissue-mRNAs and their vendor source, are as follows: 1) Normal adult brain mRNA (Invitrogen), 2) normal adult kidney mRNA (Invitrogen), 3) normal adult liver mRNA (Invitrogen), 4) normal fetal brain mRNA (Invitrogen), 5) normal fetal kidney mRNA (Invitrogen), 6) normal fetal liver mRNA (Invitrogen), 7) normal fetal skin mRNA (Invitrogen), 8) human adrenal gland mRNA (Clontech), 9) human bone marrow mRNA (Clontech), 10) human leukemia lymphablastic mRNA (Clontech), 11) human thymus mRNA (Clontech), 12) human lymph node mRNA (Clontech), 13) human spinal cord mRNA (Clontech), 14) human thyroid mRNA (Clontech), 15) human esophagus mRNA (BioChain), 16) human conceptional umbilical cord mRNA (BioChain).

TABLE 1

			272 274 276 280 284-289 292-294 297 299 303 308 310-312 316-319 322 325 333 335-339 341-345 352 355 360 362-364 374-379 389 391-392 395-396 403 414 416 418 420 422 427-430 435 443 452 455 457 459-462 467 470-473 477 485 488 490-492 495-496 499 501-503 506-507 509 511 513-514 517 519-523 527-530 533-535 539-545 547 549 554 556 559 561-564 568 570 572 575-576 579-580 583-585 588 593 595-596 599-600 603 606-609 611 613-615 617-622 626 630 635-636 638-641 644 646-648 651 656-657 660 662-665 670-671 675-677 679-680 683-684 687 689 691-701 704-708 710-713 716 719 721-722 726-734 738 744-745 748-749 751-753 756-759 761-763 765 767 771 775-776 778-779 782-786 788-792 796 798-802 805-806 813-815 817-820 823-824 827 829 833-834 837-838 842 846 849 852 860 872-873 887-888 891 894-896 900 905-906 908 910 914 918-919 922-925 928-931 933-934 936 940 943 947-948 951 955-956 958 960-961 964-967 970-973 975-976 978-980 983 985 988 998 1002 1007-1010 1014-1015 1017 1019-1020 1024-1025 1028 1032-1033 1035-1037 1040 1045-1046 1049 1057 1059 1064 1066 1069 1088 1090 1097 1099
Genomic clones from the short arm of chromosome 8	DNA from Genetic Research	EPM001	368 987 993-994 1042 1102-1103
esophagus	BioChain	ESO002	53 177 545 577 687 695 1087
fetal brain	Clontech	FBR001	9-11 52 64 85 155 221 239 284 361 392 552 700 719 744 918 941 952 1010 1098
fetal brain	Clontech	FBR004	4 35 47 76 110 288 323-324 338 350 352 373 469 490 530 852 898 905 922-923 928-929 1077 1101
fetal brain	Clontech	FBR006	3 6-7 9-11 19-20 25 30 43 46 50 52-53 55 57 64-65 70 72 75 80-82 84-85 91 95 98 100-101 104 110-111 114-117 128 134 138 141 147 150 157 162-163 169 171 182 184-187 190 193-194 199 205 212-215 219 222 225 237 243 248-250 258 266-267 272 274 281 284-286 292 300 305-306 309 312 316-318 334 336-337 339 346 351

TABLE 1

			356-357 361 371 373-376 378-379 381 383 388 392 399 404 412 416 418 420 426-428 441-444 447 459-462 464 484 491-492 495 502-503 511 524 528 543 546 549 556-557 569 575-576 579-580 583 589 597 602 608-610 622-623 625 632 637 639 642-643 645-646 648 650 654 656-658 677 679 686 688 692-694 696 701 704 710 712 717-718 720 723 730 735-736 740 745 754 756 759 771 778 798 803-804 808 820 832-838 840 842-845 849 852 856 861-862 867 873 875 877 879-889 900 905 911-912 915-916 919 921 926 935 943-945 948 950 952 956 960-963 971 977 998-999 1004 1007-1010 1016 1024-1025 1029 1031 1034 1040 1046 1059-1061 1063 1066 1069 1071-1072 1076 1082 1086-1088
fetal brain	Clontech	FBRS03	194 549 757 877
fetal brain	Invitrogen	FBT002	2 7 12 19-20 23 30-32 54-56 63 81 92-93 104 108-109 112 117-118 135 138-140 157 164 168 183 190 193 197 202 233 237-238 248-249 266-267 272 274 300 310 325-326 328 334 351-352 354 364 372-373 382-383 392 401 420 430 466 468 472-473 499-500 510 514 525-526 532 539-540 542-543 582-585 589 606 612 622-624 633 635-636 641 647-649 653 656-657 673 683 687-688 692-693 695 700 702 710-716 733 740 744 757 759 761 767 771 774 779 798 804 807 809 817 825-826 833-834 838 845-846 882-884 887 893-894 909 911 924 947 952 961 964-965 970 975-976 984 1002 1004 1007-1010 1020 1032 1034-1035 1039-1040 1045-1046 1048 1054 1059 1069 1073-1074
fetal heart	Invitrogen	FHR001	549 724 837 919
fetal kidney	Clontech	FKD001	3 44 60 65 68 76 96-97 105 110 117 129 143 174 193 197 217 239 248-249 261 277 296 300 328 332-333 336-337 339 361 403 415 464 483 506 518 529 539-540 542 549 553 563 596 616 645 647 656 677 679 695 734 776 792 818 828 975 1002 1021 1045 1059 1061 1066 1081 1093
fetal kidney	Clontech	FKD002	25 57 100-101 114 259 279 749 820 1014-1015

TABLE 1

fetal kidney	Invitrogen	FKD007	8 361 675-676 687 916 920 1010
fetal lung	Clontech	FLG001	44 71 100-101 119 147 224 236 281 293-294 303 309 327 329 393 400 403 430 470-471 517 527 534-535 549 579-580 764 867 871 889 895 918 999 1001 1035
fetal lung	Invitrogen	FLG003	6 17-18 25 46 49 52 57 82 100-101 104 106 141-142 149 157 162 167 190 206 210 220 222 224 240 258 279 300 322 339 343-345 352 355 393 400 409-410 412 445 450-451 458 490 515 537-538 549 560 608 619 624 633 636 650 675-676 702 704-705 712 715 779 786 859 874 889 904-905 913 948 980 999 1010 1032 1037 1045 1059 1071 1104
fetal lung	Clontech	FLG004	7 139-140 421 528 820
fetal liver-spleen	Soares	FLS001	2-5 15 17-18 23 25-26 29-31 33 35 43-47 49 51-57 59-60 63 65-66 73-74 76 80 82 84-86 89 91 93 96-111 113-116 118-119 122 126-128 130 133 135-144 146-153 155-157 161-162 164-165 167 174-175 177-180 183-187 189-194 197-199 201-204 206 209 211-215 217 222-224 228-229 237-238 240 243-244 247-252 255 257 259 261-274 276-282 284 287-290 292-298 300-301 303 305-312 314-318 322 325-328 333-339 341-342 346 348 351-352 354 356-357 360 363-364 366 372-377 379 384 390-393 396-397 399-403 409-412 414-415 418 420 422 424-425 427-430 432 434-435 443-450 452 456 458-461 463 467-472 477 480-481 483 485-490 493 495-497 499 503-504 506-509 511-517 519-522 528-532 534-552 554-561 563-568 572 574-580 582-583 587 589-596 599-601 603 606 608-615 617-624 626 632-637 640-645 647-648 650-652 654 656 658 661-665 667-670 673 675-677 679-680 682-684 687-689 691-696 700 702 704-707 713-714 716-719 721 723-724 727-732 735 737-738 741 743-745 747-748 750-753 756-759 761-763 765 767 771 774-776 778-779 786 788-792 796-802 804-808 810-812 814 816-817 820-823 825-826 833-839 842 848-849 852 859 864 866-867 877 879-881 884-889 891 895 897-900 903 905 907 910-911 914

TABLE 1

			916 918 924 927 931 934 936-937 941 944 948 951 956 958 960-963 967-972 974-975 977-980 984 989-990 996-998 1003-1010 1014-1015 1017 1020 1022-1023 1028 1031 1033 1035-1037 1039-1040 1043-1050 1052-1053 1055-1057 1059-1060 1062-1064 1066 1068-1071 1073-1074 1076 1079-1081 1090 1092 1094 1096-1101 1104
normalized fetal liver-spleen	Soares	FLS002	2 4 7 15 21-22 25-26 29 32 41 44 47 49-52 54-57 59-60 65-66 70-71 73-74 76 84-87 95 97 100-101 103-104 107-110 112 114 117 119 122 125-126 128-129 134-137 139-141 143 145-147 149-150 152-153 155-157 161 164-165 167-168 171 174-175 177-179 183-187 189-191 193-194 199 201-206 209 212-217 219 222 227-229 231-232 234 237-238 240-243 247-253 259-263 266-267 269 271-272 274 278 281-283 285-290 293-294 296-301 303-310 312 315-320 322 325 327-330 332 334-338 341-346 348 351-354 356-357 363-364 367 370 372 378 380 382-385 389 391-393 396 400-401 403-405 407-408 412 415-416 418 421-422 426-429 432 436 438 443 447-450 452 454 457-461 464 466 468 470 475 479-483 486-487 490 493 496-497 503 508-509 511-512 517 519-522 524 528 531 533-541 543-546 550 552 554 556 558-559 561 563 566-567 572 574 577 579-583 586-587 589 591-593 597 600-602 606 608-611 613-619 621-622 624 626-628 630 633-634 637 640 645 648 652-654 658 660-662 664-666 668 671-672 677 679-680 682-684 686 688 691-693 695 697-699 701 704 708 711 713 715-719 721-723 727-730 732-733 737 741 744-745 747-748 751 753-754 756-759 761-763 768 771 776 778 782 786 788-792 794-796 798-803 812 814-816 821-823 829 832-834 837-839 845 847 849 852 861-862 866-867 870-873 879-881 884-886 888 893 895 897 900 903 905 908 916 918 920 924-925 927 930-931 933 935 937 946 948 950-951 954 958 960-961 965 968-969 974-976 978-979 989-991 996 998 1002 1004 1007-1009 1013-1015 1017-

TABLE 1

			1020 1024-1025 1029 1033-1037 1039-1040 1044-1045 1047 1050 1052-1053 1055-1057 1059 1062 1066 1068-1070 1076 1079-1081 1084 1090 1094 1097 1100
fetal liver-spleen	Soares	FLS003	25 45 52 54 57 65-66 76 96 98 103 108-109 114 118 127 177 189 219 268 665 753 1014-1015 1017 1023 1047 1059 1068
fetal liver	Invitrogen	FLV001	2 17 29 44 47 49 52-55 68 82 86 88 93 103 108-109 115-116 139-140 164 168 178-180 183 197 202 209 227-228 231 238 243 245-246 248-250 284 309 336-337 349 351 354 367-368 384 401 409-410 416 432 443 445 462 468 470 494 502 514 522 542 546 557-558 560 566 574 579-580 594 596 603 641 650 654 661 664 673 675-676 680 682 684 687 692-693 696 702-703 708 730-731 759 775-776 778-779 807-808 811 833-834 837 842 846 848 872 884-885 916 940 947-948 952 957 970 975 997 1002 1004 1007-1010 1034-1035 1039-1040 1045 1052-1053 1094 1096
fetal liver	Clontech	FLV002	358 685
fetal liver	Clontech	FLV004	28 47 52 230 257 278 361 522 532 544 812 926 960 1003 1014-1015 1017 1045 1057
fetal muscle	Invitrogen	FMS001	32 34 49 52 56 71 86-87 93 104 110 122 126 136-137 147 151 177 193 204 237 245-246 266-267 274 284 300 303 313 325 339 354 398 409-410 414 417 445 459-461 472 511 522 545 559 600 602 608 622 657 667 673 675-677 679 687-688 695 702 715 723-724 733 749 753 759 772 786 788-791 805-806 810 853 862 887 897 917 930 948 956 960 967 988 1007-1010 1014-1015 1019 1026-1027 1059 1073-1074 1089-1090 1094 1100
fetal muscle	Invitrogen	FMS002	75 100-101 137 222 276 420 554 687 721 772 956
fetal skin	Invitrogen	FSK001	1 3 6-8 12 14 18 24-25 28-29 31-32 35 41 43 45 49 52-55 57 61 67 78-79 82-83 85-86 93-94 98 100-101 110 115-116 119 122-123 128 136 139-140 146 150 164 167 178 180 183 189-191 193 195 201 206 212-215 222 224 231 236-237 243 248-249 257 260 265 271 288-289 292 300 308-309 313 325 327 329 336-337 339 343-346 349 351 354 358 360 363 370 383

TABLE 1

			386-387 391-392 396 400-401 404-405 409-410 412-413 416 432 434 437 443 448 450 454 459-461 464-465 470 472-473 483 494 496 499 501-502 507 509-511 516 527 542 544 546 548-549 566 579-580 593 595-596 603 605 609-610 615 619-620 622 624 633 635-636 640 647-648 653-654 657 662 664 673 677 679-680 686-687 691 695 701 706 713 715 720 723 729-731 743 746-747 749 751-753 758 761 766 779-780 786 788-792 797 802 808 812 817 820 823 829 837-838 841-842 845 852 856 867 871 878 881 884-885 887 890-894 897 900-901 905 908-909 911 914 918 930 933 948 956-957 964 967 970 972-975 989 1000 1007-1012 1014-1015 1019-1020 1032 1034 1036 1039-1041 1044-1047 1055-1056 1059 1061 1063 1066 1068 1070 1073-1074 1077 1089-1090 1096 1101
fetal skin	Invitrogen	FSK002	3 8 12 14 27 43 45 58 73 75 82 88 100-101 107 110 124 128 189 219 261 275 451 495 530 626 765 798 844 1007-1010 1016 1023-1025 1033 1037 1040 1059-1061 1067-1068 1081 1087
fetal spleen	BioChain	FSP001	26 265 598 614 797
umbilical cord	BioChain	FUC001	6-8 18 24 29 41 44-46 52-53 59 63 65 67 77 80 82-84 86 88 90 94 98 101 104-110 112 118-120 128 133 135 137 141 147 156-157 160 162 164 169 178 183 199 201 212-215 222 230-231 237 250-253 264-267 269 283 292 297-298 310 315 323-325 328 338-339 343-345 349-350 356-357 366 369 378 380 383 385-387 391 394 397 403-404 409-411 416 433-434 446 449 455 459-461 464 473-475 477 480 487-488 499-502 507 518 528 530 533 543 546 549 560 564 573 579-580 582-585 588 591-592 596 599 612 617-620 623 627 635 640 647 653 664 671 677 679 685 687-688 692-693 695 704 711 713 725 734-735 748 750-752 762 765-766 778 783-786 801-802 804 823 833-837 840 843 845 852 860 886 893-894 897 905 907 913 924-925 933-934 936 969 973 976-977 988 1006 1010 1034 1036 1040 1047 1049 1061 1063 1065

TABLE 1

			1071 1088 1090 1094 1099
fetal brain	GIBCO	HFB001	3-4 12 14 19-22 25 27 29-32 35 37-38 44-45 50 52-53 55 57 60 63 73 82 88-90 93 98 105 108-109 112 115-117 123 125 127-129 131-137 144 146-147 149 151-152 156-157 160-162 164-165 167 170 173-174 176-178 180-181 183-186 190 193-194 197 200-201 204-205 212-215 218-219 221-222 231 242-243 245-246 248-258 261 264 266-267 269 272 276 278 281 283-286 288-289 291-297 299-301 308 310 314 321 323-325 328-330 332-333 338 340 346 349-350 352-354 358 360 363 369 371 374-376 379 381 392-393 397 401 405 411 413-416 418 420 422 427-430 434-435 443 447 450 454 456 459-461 468 473 475 480 484 487-490 495-496 499 504-506 509 511 515 519-522 524-535 539-541 543-545 547 549 554 556 561-562 564 568 571-572 575-576 578-580 583-586 590 593-595 597 599-603 606 609-610 612 614 617-620 622-625 635 639-647 650-651 654 656-659 662 665-666 668 670 673-674 677 679 682 684 686-689 692-697 699-701 704 706-707 711 714 717-719 721-723 726 729 735 738 741-742 746 748 753 757 759 761-762 767-768 770-771 775 778 783 786 792 796-798 802-804 810-811 816 823-824 827 829 832 837-840 842 845-846 848 856 859 864 882-883 889 891 896-898 900 905 908-909 915-916 919 922-924 930-931 933 936 939-941 943-944 948 957-958 961 966 969 972 975-979 983-984 995 997-998 1002 1006 1010 1017 1028-1029 1031-1034 1036 1039 1045-1047 1049 1055-1056 1059-1060 1063-1065 1069 1076 1079 1084 1088 1100 1104
macrophage	Invitrogen	HMP001	177 312 360 544 563 620 675-676 1069
infant brain	Soares	IB2002	3-4 6-7 12 19-20 22 25 29-30 35 44-45 50 52-53 56-57 65 70 74 80 82 85 87-88 90 92-93 96 102 104-105 108-109 112 117 123 127-128 135 138-140 143-144 146-147 149-150 152 156-157 161 164 166 168 171 177 181-182 184-187 190 193-194 199-201

TABLE 1

			205-209 211-215 222 225-226 237 239-240 242-243 248-252 255 257-258 260-263 266-267 269 272-274 284-286 288-290 293-294 297 299-301 304 309 315 319 323-325 328-334 336-337 339-340 343-346 348-357 371 373 377 379 381 385 389 396-398 401 405 412-415 417-420 423 427 429 435 439 443 447 453-454 456 462 464-465 469 472-473 477-478 484 488 493 496 499 510-511 515 519-521 525-528 530 533-535 539-540 545 547 549-550 555 557 560-561 563 571 573 575-576 579-581 583 588-589 597 603-604 606 609-612 614-615 617-619 621-623 625 628 632-633 635-637 640-641 646-649 653-656 664 666 668 673-677 679 684 686-687 691-694 702 704 706-707 712-713 721 724 735 739-740 743-744 746-748 752-753 757-759 762 770-771 774 778 797-802 807-809 812-813 819 821-827 829 838 840 842-843 852-859 861 863-864 872-873 877 879 882-883 885-886 888 893 897-898 900 907-911 915-916 919 921 924 931 937 939 941 946 948 951-952 959 964 969 971 973 975 977-979 984-985 995 997 1003-1004 1006-1010 1019 1022 1031-1032 1035 1039 1046 1052-1053 1055-1056 1058-1060 1064 1071 1073-1074 1078 1090 1094 1097-1098 1104
infant brain	Soares	IB2003	4 7 12 19-20 22-23 25 30 44 49- 50 55 57 76 82-83 88-89 127-129 146 150 152-153 164 177 181 190 194 205 209 211-215 226 239 248-252 261 263 266-267 269 272-273 278 283 289 293-294 297 299-301 328 330-331 340 346 348 352-353 356-357 360 371 398 401 411-412 414 418 443 459-461 464-465 469 480 491-492 496 509 530-531 549 554 560 567 574 579-580 583 589 597 604 606 608-610 619 622-623 633 637 641 649 664 666 684 686-687 692-693 697 699 705 712 721 725 731 744 746 798 803-804 809 812 816 833-834 838 840-842 849 856 859 863 882-883 885 888 891 895 898 909-910 915 918-919 930-931 941 948 974 978-979 995 1004 1017 1023 1034 1037 1040 1046-1047

TABLE 1

			1055-1056 1068-1069 1078 1090 1094
infant brain	Soares	IBM002	47 50 226 239 285-286 331 338 348 499 641 692-693 717-718 819 853 898 948 984 995 1010 1017 1087
infant brain	Soares	IBS001	7 44 120 226 239 300 330 349 351 353-354 504 636 653 802 819 840 877 882-883 885 919 948 955 961 977 1007-1009 1014-1015 1032
lung fibroblast	Strategene	LFB001	6 29 43 101 104 110 120 136 146 167 172 177 190 193 202 210 212-215 217-219 238 241 243 262 276-277 284 292 308 325 343-345 374-376 395 403 429 432 459-461 478-480 495 522 528-532 534 539-541 554 561 588 621 640 642-643 651 662-663 671 687 692-693 695 712-713 721 727 741 753 759 761 771 801-802 823 825-827 829 884 912 918 922-923 936 969 975 985 1001 1010 1024-1025 1033
lung tumor	Invitrogen	LGT002	2 5 14-15 17-18 21 25 31-33 36 41 43-44 49 53-54 57 62-63 71 73 77 83 88 97 100-101 104 106-110 117-118 124-125 128 136 142 146-151 154-157 161-162 164-165 167 170-172 174 177-180 183-186 189-190 193 196-198 201 205 209 216 219 222 229 231 233 240 242-243 248-252 261-262 264-265 272-273 278 284 288-289 292 296 298 300 303 307-308 310-311 322 325 327 329 334-335 339 343-346 349 351 354 365-366 378 382 388 392-393 396 399-400 402-403 406-407 412 418-423 427 434 436 447 449-450 457-462 468-469 471-473 475 481 485 487-488 494-497 499 509 511 513-514 517 523-524 526-530 534-535 537-540 542-546 549 551 559 563-565 567 572 575-576 582-583 587 589 591-592 595 597-598 603 605-607 609 611-612 614 617-619 621-622 624 634 637 640 642-643 648 650 653-654 656 658 664-666 668 671 673-674 677 679-680 682 684 686-688 692-695 697 700-701 706 708 710-712 714 717-718 721 726 729 733 735-738 740 743-744 748 752-753 756-760 762-763 767 774 776 778 784-786 793 795-796 798 801 805-806 808 815 823-824 828

TABLE 1

			830-831 833-834 837 841-842 845-847 856 859 861 867 884-885 887-889 891 893 897 903 905 908 911 916 924 931 937 942 947-948 955 957-960 966 968 970-971 973 975 978-979 985 990 995 998 1002 1007-1011 1019 1028-1029 1031 1034-1036 1039-1041 1043-1045 1047 1055-1056 1059 1068-1069 1073-1075 1084 1087 1090 1092 1094 1099
lymphocytes	ATCC	LPC001	12 21 25 30 44 55 57 63 73 77-78 86 88 95 97 100-101 104-105 119 121-122 125 128-129 149 177 190 201-202 205 212-215 224 232-236 239 250 253 265 279 290 292-294 298 300 305-306 308 314-315 325 327 333 336-338 341-342 372 379 401 407 439 448 459-461 464 470 473-474 477 485 487 507 523 534 551 554 561 566-568 577 583 591-592 596 608-610 615 662 677 679 683 688 691-695 721 738 743 767 796 824 829-830 832 837 847 852 866 888 894 905 915 921 926 931 934 940 948 950 955 959-961 980-983 998 1002 1007 1009-1010 1029 1035-1036 1038 1040-1041 1047 1057 1059 1069 1071 1073-1074 1076-1077 1079 1084 1087 1096
leukocyte	GIBCO	LUC001	1-3 6-7 13-15 21-22 25 27-31 43-44 53-58 60-61 73 77 79 82-84 86 88-90 95-99 104-105 108-109 111 113 115-116 119-125 127-128 130 133 135-138 142-146 148-153 155 157-159 161-165 170 173-175 177-178 183-187 190-193 197 201-202 204-206 209 211-215 217 222-224 228-230 232-235 242-243 247 250-253 255 258 260-262 265 269 272-274 278-279 281 283-284 288-290 292-298 300 304-306 311 314-315 320 322-328 333-334 338-339 341-346 349 351 356-357 360 364-366 374-378 380 382 388 390 392 399-404 409-410 413-420 422-423 427-430 433 435 437 440 443 449-450 452 454-462 464 468-470 472-474 477 480 483 485 487-488 495-496 499 502 504 511 513-515 517 519-521 523 528 530-545 548-549 551-556 562-564 566-577 579-581 583 587 589-601 603 606-612 614 617-619 622-623 628-629 632 635-636 640 642-643 645 647-649 651 654 657-658 660

TABLE 1

			662 664 672-677 679-680 682-683 686-689 691-697 699 702 705-707 710-711 713 715 717-719 721-724 726 729 731 735 738 741-743 747-748 750-751 753 757 759 761 767 774-775 778-780 782 786 795-796 799-802 804-806 811-812 814 818 821-822 824-826 829-834 841 847 852 857 859-863 865-867 869 871-872 875 884 887-889 891 894-895 900 905 908-910 912-916 920-926 928-932 937 942 944 946 948 951-952 954-955 959-960 962-965 967 970-974 977-983 989-990 996 998 1002-1003 1007-1010 1012 1014-1020 1023-1025 1029 1031 1033-1037 1039 1043-1047 1049-1051 1055-1057 1059-1060 1063-1064 1067 1069-1071 1076-1077 1084 1090 1094 1100
leukocyte	Clontech	LUC003	45 78 104-105 129 135 150-151 155 177 212-215 229 251-252 257 265 285-286 298-299 301 308 310 325 343-345 351 361 380 400 448 457 459-461 487 533 536 541-542 564 590-592 602 636 639 677 679 689 802 808 859 872 905 926-927 931 965 1036 1043 1047 1049 1067
melanoma from cell line ATCC # CRL 1424	Clontech	MEL004	9-11 18 24 45 53-54 56 60 86 89-90 104 119 122 128 130 141 155 164 173 177 201 203 221 223 243 251-252 264 278 290 292 325 339 341-342 346 418-419 421 443 462 471 474 485 517 530 541 544 554 563 568 572 590 601 619 621 645 663 672 677 679 686-687 713 719 726 738 744 757 763 777 788-791 796 825-827 838 845 852 861 879 884 889 903-904 906 915-916 925 928-929 934 943 968 970 983 1001 1010 1020 1024-1025 1035 1045 1057 1076-1077 1084 1094 1097
mammary gland	Invitrogen	MMG001	1-2 4-5 7 12 14 17-18 21 23 29 32-33 35-36 41 44 49 52-56 61 63 66-68 70-71 79 82 86 88-89 97 104 108-111 115-118 122 125-129 136-138 148 150 153 156 159-160 162 164 168-169 172 177 180 183-186 190-191 193-194 197 202 204 209 212-216 222 224 229 231 233 238 248-250 263 265-267 274 279 284 295 300 305-306 310 312-318 322 325-326 328-330 334 336-337 339 341-342 346 349

TABLE 1

			351-354 356-358 361 364 370 377-378 388-389 392 396 400-401 404 406-414 416-418 420 422 427 431-432 434 439 443 445 450 454 464 468 470-473 478 488 491-492 494 499 502-507 512-514 522 527 539-543 548-549 551 554-555 557 563 566 574 578-585 589 591-592 596 603 606 608-610 613 622-624 633 635-636 640-641 644 647-648 650 652-653 657 664-665 671-676 680-684 687-688 692-694 696 701-702 704-705 711 713 715 720-721 724 727 731 733 744 746-747 752 757-764 766-767 774 776 778-780 784-791 796-797 801-808 810-812 820-822 825-826 828-831 833-834 837-838 842 848 856 859 861-862 872-874 879-881 885-888 896-897 901 905-907 911-912 914 921 924 930-931 937 943-944 948-949 951-952 960-970 973 975-976 988 997 1004 1006-1010 1013-1015 1020 1024-1025 1032-1035 1039-1042 1044-1045 1049 1059-1060 1067 1069 1071 1073-1074 1079 1096
induced neuron cells	Strategene	NTD001	3 13 31 44 48 50 53 55 96 98 166 171 207-208 217 221 224 242 262 272 289 323-325 332 418 459-462 464 476 484 506 511 541 543 560 623 640 672 677 679 729-731 744 761 793 882-883 895 912 936 943 964 978-979 981 984 1001 1010 1039 1049 1103
retinoid acid induced neuronal cells	Strategene	NTR001	56 105 180 300 359 415 686-687 888
neuronal cells	Strategene	NTU001	5 7 9-11 48 64 66 80 88-90 128 139-140 144 162 177 180 184-186 193 212-215 248-250 274 279 284 300 325 340 382 384 399 427 455 476 543 589 635 641 664 687 692-693 713 753 757 811 837 874 908 915 924 936 961 973 985-986 1001 1007-1010 1019-1020 1040 1045 1055-1056 1068 1073-1074 1090 1103
pituitary gland	Clontech	PIT004	52 82 93 104 128 744 784-785 962-963 1002 1010 1068
placenta	Clontech	PLA003	43 528 591-592 970 1007-1009 1059
prostate	Clontech	PRT001	3 31 46 55-56 73 104 108-110 135-136 143 151 163 171 174 179-180 187 196 201 206-208 222 295 327 333 336-337 343-345 392

TABLE 1

			413 451 455 473 505 546 556 559 575-576 590 597 625 632 650-651 675-676 689 713 721 733 742 750 784-785 801 814 831 885 887 891 922-923 931 948 962-963 977 985 1003 1023 1031 1034 1039 1050 1052-1053 1057
rectum	Invitrogen	REC001	14 17 41 46 61 68 82 88 94 104 115-116 120 122 138 142 157 191 212-215 222 243 261 265 279 300 305-306 310 323-325 329 336-337 351 401-403 405 409-410 422 432 434 440 446-447 450 454 458 474 504 510 528 534 536 566 588 594 598 635-636 647 673 683 708 711 721-722 753 756 759 764 775 797-798 802 819 828 842 848 861 867 874 876-878 894 909 914 930 934 961 1007-1010 1013 1024-1025 1040-1041 1045 1059 1063 1065
salivary gland	Clontech	SAL001	6 24 27 33 84 111 122 147 161 168 170 175 210 230 245-246 248-249 266-267 301 314 329 443 446 448 452 455 472 485 494 511 533 550 564 591-592 612 620 650 704 708 713 728 734 744 755 792 839 861 870 924 971-972 978-979 988 1005 1010 1023 1026-1027 1036 1049 1063 1069
skin fibroblast	ATCC	SFB001	1010 1090
skin fibroblast	ATCC	SFB002	420 713 943
skin fibroblast	ATCC	SFB003	391 808 1040
small intestine	Clontech	SIN001	7 13 44 71 82 86 88 90 97 100-101 104 108-109 119 126 128 152 177 190 193 196 198 218 222 224 230 235 239 245-246 261 268 281 288 303 305-306 310 328 338 363 392-393 397 402 434 448 464 483 514 527 542 544 551 572 577 579-580 586 589 591-592 599 606 622 684-685 687 695-696 714-716 732 744 778 786 805-806 820 837 858 888 908 924 937 954 969 1006 1010 1016 1031 1033 1039 1041 1064 1077 1088 1090 1094 1098
skeletal muscle	Clontech	SKM001	2 34 86 88 98 114 126 133 144 162 177-178 212-215 325 339 355-357 398 457 464 470 481 515 590 609 637 650 669 677 679 708 735 752 804-806 810 823 917-918 958 974 988 1011 1019 1026-1027

TABLE 1

			1033 1100 1104
skeletal muscle	Clonetech	SKMS03	1100
spinal cord	Clontech	SPC001	45 52 60 65 93 100-101 104 107 122 141 147 161 163 180 183 187 193 199 201 212-215 218 222 224 226 231 235 243 245-246 269 284 293-294 300 302 307 315 327-328 330 336-337 352-353 355 361 363-364 391 394 398 400 403 412-413 418 433-434 437 459-461 465 473 475 494 505 517 519-521 532-534 539-540 543 546 549 556-557 560 569 583 591-593 604 606 611 621 629 631 657 672 677 679-680 685 701 727 741 748 754 761 764 766 771 774 786 792 798 805-806 817 823 840 859 863 881-883 904 914 931 933 973 984 997 1002 1010 1013 1017 1020 1040 1043-1044 1046 1049 1058 1065 1090 1097-1098
adult spleen	Clontech	SPLc01	21 98 100-101 105 530 551 1010 1020 1023 1034 1045-1047 1061 1077 1087
stomach	Clontech	STO001	31 35 77 100-101 104 120 136 149 153 210 274 297 308 329 343-345 406 423 464 466 469 531 606 647 651 653-654 663 696 700 720 730 752 760 824 859 897 924-925 949 967 970-971 1012 1039 1049 1059
Mixture of 16 tissues-mRNAs*	Various Vendors*	SUP002	4 37-38 47-48 94 108-109 472 544 859 1010 1016 1102
Mixture of 16 tissues-mRNAs*	Various Vendors*	SUP005	88 99 108-109 115-116 195 547 1010 1064 1078
Mixture of 16 tissues-mRNAs*	Various Vendors*	SUP008	19-20 24 82 98 104 115-116 157 326 705 852 952 1068 1073-1074
Mixture of 16 tissues- mRNAs*	Various Vendors*	SUP009	12 43 104 472 850-851 1010 1040 1043 1090
thalamus	Clontech	THA002	6-7 14 24 29 37-38 52 61 66 69 93-94 115-116 132 151 157 182 200 206 224 243 283 285-286 325 333 348 363 398 409-411 420 458

* The 16 tissue-mRNAs and their vendor source, are as follows: 1) Normal adult brain mRNA (Invitrogen), 2) normal adult kidney mRNA (Invitrogen), 3) normal adult liver mRNA (Invitrogen), 4) normal fetal brain mRNA (Invitrogen), 5) normal fetal kidney mRNA (Invitrogen), 6) normal fetal liver mRNA (Invitrogen), 7) normal fetal skin mRNA (Invitrogen), 8) human adrenal gland mRNA (Clontech), 9) human bone marrow mRNA (Clontech), 10) human leukemia lymphablastic mRNA (Clontech), 11) human thymus mRNA (Clontech), 12) human lymph node mRNA (Clontech), 13) human spinal cord mRNA (Clontech), 14) human thyroid mRNA (Clontech), 15) human esophagus mRNA (BioChain), 16) human conceptional umbilical cord mRNA (BioChain).

TABLE 1

			466 468 478 512 568 575-576 584-585 648 684 686-688 691 694 722 744 786 818 833-834 839-840 846 861-862 866 882-883 897 909 939 970 995 1035 1045 1059
thymus	Clonetech	THM001	3 6 15 24 31 44 84 104 119 139- 140 142 145 157 161 167 177 180 183 191 201 210 212-215 221 223 229 231 243 260 262 266-267 281 289 298 316-318 323-325 327 335 339 346 352 380 392 400 404 412 419 423 430 443 446 450-451 459-461 464 468-469 481 485 487 494 509 511 513 530 536 543-544 549 551 555-556 563 569 572 577 584-585 598 614 617-618 654 670 673 677 679 686 702 717-718 721 748 755 762 792 796 802 805-806 808 829-831 847 852 861 866 884 895 898 902 905 907-908 910-911 916 961 967 972 1010 1019 1039 1057 1059 1073-1074
thymus	Clontech	THMc02	7 15 23 25-26 33 43-46 55 57 73 76 84 88-90 98 104-105 110 119 128-130 135 138-141 144 146 148-150 157 162 171 174 178 180 187 190 193-194 199 201 205-206 209 212-215 224 229-230 241-242 245-246 248-249 251-253 262-263 272 280-281 283 289 308-310 312 314 325 328 333 336-339 347 349 351 355-357 360 380 382 385 390 400 404 409-410 415 422-423 427-428 434-437 441 443 447-449 451 456-463 471 473-474 481 483 485 495 508 514 519-521 526 533 539-541 544 546 549 555-556 566 575-576 583 593-594 598 600 615 620 628 636 645 648 650 654 656 662 668 673 675-677 679 686 695-696 702 704 727 729 762-763 768 778 786 798 803-806 811 820 829-830 833-834 852 861 864-866 875 885 887 895 900 905 909 912 916 924-933 951-952 957 961 970-971 974 980 998 1007-1010 1012 1014-1015 1017 1020 1024- 1025 1029 1036 1040-1041 1045 1047 1050 1060 1064 1067-1069 1076 1079-1080 1082 1087 1090 1092-1093 1097-1098
thyroid gland	Clontech	THR001	5 8 14-15 17 21 23 27 31-32 36 41 44-46 55-56 58 67 71 73-74 85 88-89 95 98 104-105 107-110 117-120 124-126 128-129 132 146-148 150-152 156 158-159

TABLE 1

			161-162 164-168 170-171 174-175 177-178 180 183-187 190-191 193 199 201-202 204 210-215 222 224 238 240 245-246 251-252 264 270 272 278-279 281 283 287 289 292-294 296-300 305-306 308 312-313 320 325 327-329 333 339 343-346 348 350 352 363 372-376 378 380 382 391 393 405 411-413 416 418 422 424-425 427 429 434 443 445 447 449 454 457 464 469 479-480 483 487 489 508-509 511 513 518 523 526-530 532 534 542-545 552 559-560 563 565-566 572-573 575-577 579-580 583 593 595-596 600-601 609-610 613-614 616 619-621 624 626 628-629 635 640 644 648 650-651 653 665-666 668-669 674 677 679 688 691-693 698 702 708 712 721 726-727 732 735 738 740-741 743 745 747 757 759-760 766-768 777 783-786 794-795 801-802 805-806 813 815 817-818 820 823 825-826 831-832 835-836 838-839 845 850-853 856 859-862 866-870 879 881 886 889 893 897-898 903 906 908 911 920 922-923 925 931 935 937 944 947-948 950 952 961-963 973 976-979 989 996 1004 1010 1020-1022 1024-1025 1032 1035 1039 1055-1057 1060-1062 1064 1071 1084 1098
trachea	Clontech	TRC001	4 25 45 50 57 88 98 119-120 128 146 148 165 170 236 255 264 269 274 284 289 303 363 384 403 495 544 551 563 579-580 599 603 609 619 622 734 764 769 788-791 802 897 904 918 922-923 927 971 1002 1075 1077 1096
uterus	Clontech	UTR001	60 82 94 112 120 122 126 147 165 167 173 177 180 187 193 197 201 205 217-218 236 278 287 310 338 346 404 435 457 464 518 530 542 557 562 599 616 621 624 683 697 699 706 738 764 796 813 859 908 948 969 977 1000 1010 1013 1033-1034 1065

TABLE 2

SEQ ID NO	CORRESPONDING SEQ ID NO. IN U.S.S.N. 09/552,317	ACCESSION NUMBER	DESCRIPTION	SMITH-WATERMAN SCORE	% IDENTITY
1	152	AL122081	Homo sapiens hypothetical protein	1930	100
2	167	AF212921	Mus musculus MMTV receptor variant 1	484	94
3	205	Z75330	Homo sapiens nuclear protein SA-1	6492	99
4	210	AL008583	Homo sapiens dJ327J16.3 (supported by GENSCAN, FGENES and GENEWISE)	2133	99
5	225	AK000381	Homo sapiens unnamed protein product	1028	98
6	226	AK000418	Homo sapiens unnamed protein product	1747	100
7	264	AF156598	Mus musculus p53-regulated DDA3	997	65
8	268	AK001463	Homo sapiens unnamed protein product	1131	100
9	293	AB033039	Homo sapiens KIAA1213 protein	2438	100
10	293	AB033039	Homo sapiens KIAA1213 protein	1510	74
11	293	AB033039	Homo sapiens KIAA1213 protein	2415	98
12	302	AK001184	Homo sapiens unnamed protein product	2830	99
13	311	AB021643	Homo sapiens gonadotropin inducible transcription repressor-3	2761	99
14	352	AL122089	Homo sapiens hypothetical protein	593	100
15	358	AC007228	Homo sapiens BC37295_1	1178	44
16	368	L29154	Homo sapiens immunoglobulin heavy chain VDJ region	439	84
17	393	AB037780	Homo sapiens KIAA1359 protein	1439	74
18	477	AK000404	Homo sapiens unnamed protein product	1177	99
19	508	L22557	Rattus norvegicus calmodulin-binding protein	1949	85
20	508	L22557	Rattus norvegicus calmodulin-binding protein	2363	92
21	515	AK002158	Homo sapiens unnamed protein product	1588	99
22	578	AL080076	Homo sapiens hypothetical protein	107	30

TABLE 2

23	588	AJ251516	Mus musculus cysteine and histidine-rich protein	1460	99
24	591	AL117551	Homo sapiens hypothetical protein	1773	100
25	593	AB033076	Homo sapiens KIAA1250 protein	6286	100
26	594	AK000625	Homo sapiens unnamed protein product	721	100
27	619	AF161420	Homo sapiens HSPC302	2623	97
28	620	AL117477	Homo sapiens hypothetical protein	2551	100
29	654	AK001782	Homo sapiens unnamed protein product	1161	100
30	692	D25217	Homo sapiens KIAA0027 protein	1911	100
31	753	AB041581	Mus musculus unnamed protein product	1758	95
32	758	X03414	Drosophila melanogaster Kr polypeptide	316	45
33	787	AF151079	Homo sapiens HSPC245	643	100
34	833	AK000643	Homo sapiens unnamed protein product	614	53
35	838	AB029022	Homo sapiens KIAA1099 protein	1095	61
36	870	AF213465	Homo sapiens dual oxidase	2016	100
37	891	AF181562	Homo sapiens proSAAS	1319	100
38	891	AF181562	Homo sapiens proSAAS	1024	99
39	921	AB020671	Homo sapiens KIAA0864 protein	5438	99
40	924	AB033051	Homo sapiens KIAA1225 protein	4438	100
41	932	AB011105	Homo sapiens KIAA0533 protein	8255	100
42	942	AB032983	Homo sapiens KIAA1157 protein	2231	100
43	958	AF139077	Homo sapiens M5-14	1463	98
44	968	AK001366	Homo sapiens unnamed protein product	2940	97
45	992	AF198454	Homo sapiens epithelial protein lost in neoplasm beta	3927	100
46	1025	AK001753	Homo sapiens unnamed protein product	217	68
47	1074	AF169017	Homo sapiens formiminotransferase cyclodeaminase	2717	98
48	1104	A95106	unidentified RED ALPHA	1202	99
49	1114	AL137479	Homo sapiens hypothetical protein	1942	100
50	1144	AF072372	Mus musculus lysosomal trafficking regulator 2	3388	97

TABLE 2

51	1262	M14912	Homo sapiens pol	132	86
52	1318	AF090934	Homo sapiens PRO0518	382	100
53	1319	X66363	Homo sapiens serine/threonine protein kinase	2499	100
54	1328	AF072758	Mus musculus fatty acid transport protein 3; FATP3	2097	87
55	1436	AB014514	Homo sapiens KIAA0614 protein	8406	100
56	1464	AE003453	Drosophila melanogaster CG10509 gene product	654	51
57	1584	AB033076	Homo sapiens KIAA1250 protein	6286	100
58	1617	AB033067	Homo sapiens KIAA1241 protein	4229	99
59	1724	D88585	Chlorocebus aethiops hepatitis A virus receptor	401	36
60	1728	AF208845	Homo sapiens BM-003	1375	99
61	1772	AB015427	Homo sapiens zinc finger protein 219	3934	100
62	1809	X57821	Homo sapiens immunoglobulin lambda light chain	797	76
63	1868	AF043695	Caenorhabditis elegans Similar to mitochondrial carrier protein	555	43
64	1898	AB033039	Homo sapiens KIAA1213 protein	2438	100
65	1926	AK000279	Homo sapiens unnamed protein product	3271	99
66	1965	AF178432	Homo sapiens SH3 protein	3700	100
67	1967	AB033099	Homo sapiens KIAA1273 protein	3082	99
68	1995	AF181721	Homo sapiens RU2S	2254	100
69	2005	AL133093	Homo sapiens hypothetical protein	2241	100
70	2027	U48238	Mus musculus zinc finger protein neuro-d4	749	63
71	2055	AL133105	Homo sapiens hypothetical protein	1783	99
72	2103	AB032958	Homo sapiens KIAA1132 protein	9116	100
73	2106	AE003528	Drosophila melanogaster CG5018 gene product	472	25
74	2166	AK001713	Homo sapiens unnamed protein product	5323	99
75	2175	AB010266	Mus musculus tenascin-X	10246	64
76	2176	AE003746	Drosophila	363	40

TABLE 2

			melanogaster CG5986 gene product		
77	2194	AL163206	Homo sapiens protein with homology to KIAA0790	1944	100
78	2236	AB033020	Homo sapiens KIAA1194 protein	2918	99
79	2250	AL122081	Homo sapiens hypothetical protein	1930	100
80	2300	AL133572	Homo sapiens hypothetical protein	3303	100
81	2323	AB033107	Homo sapiens KIAA1281 protein	3228	100
82	2340	AB030183	Mus musculus contains transmembrane (TM) region	380	42
83	2371	Z18361	Ovis aries trichohyalin	184	32
84	2399	AJ010045	Mus musculus guanine nucleotide-exchange factor	1470	58
85	2411	AF176529	Mus musculus F-box protein FBX13	2072	94
86	2428	AF210842	Homo sapiens HARP	4880	100
87	2430	AL031658	Homo sapiens dJ310013.7 (novel protein similar to H. roretzi HRPET-3)	776	98
88	2439	X57398	Homo sapiens pm5 protein	6131	99
89	2447	AE003779	Drosophila melanogaster CG2118 gene product	1670	62
90	2461	AL122097	Homo sapiens hypothetical protein	3213	99
91	2487	AE003801	Drosophila melanogaster CG14490 gene product	247	38
92	2492	AB033072	Homo sapiens KIAA1246 protein	4087	99
93	2512	AB033103	Homo sapiens KIAA1277 protein	5252	99
94	2564	AF117946	Homo sapiens Link guanine nucleotide exchange factor II	2363	100
95	2678	AL133087	Homo sapiens hypothetical protein	4159	99
96	2816	AK001529	Homo sapiens unnamed protein product	1420	99
97	2818	AL137530	Homo sapiens hypothetical protein	433	94
98	2819	AB028942	Homo sapiens KIAA1019 protein	7437	98
99	2943	AF189722	Homo sapiens PDZ-binding kinase	1688	99
100	3137	AE003450	Drosophila	681	48

TABLE 2

			melanogaster CG2221 gene product		
101	3137	AE003450	Drosophila melanogaster CG2221 gene product	716	38
102	3160	AK000708	Homo sapiens unnamed protein product	1103	99
103	3323	Y07829	Homo sapiens RING finger protein	2201	99
104	3360	AB007931	Homo sapiens KIAA0462 protein	11741	99
105	3362	U41387	Homo sapiens Gu protein	4021	99
106	3417	AF023674	Homo sapiens nephrocystin	3783	100
107	3418	AF146760	Homo sapiens septin 2-like cell division control protein	2284	100
108	3442	Z66524	Caenorhabditis elegans Homology with Squid retinal-binding protein (PIR Acc. No. A53057)~cDNA EST yk463d10.3 comes from this gene~cDNA EST yk663h12.3 comes from this gene	1190	48
109	3442	Z66524	Caenorhabditis elegans Homology with Squid retinal-binding protein (PIR Acc. No. A53057)~cDNA EST yk463d10.3 comes from this gene~cDNA EST yk663h12.3 comes from this gene	848	42
110	3444	M26576	Homo sapiens alpha-1 type IV collagen	9412	99
111	3855	AF113536	Homo sapiens MO25 protein	1381	81
112	3863	AJ271385	Homo sapiens UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 8	733	46
113	4090	AF105228	Bos taurus tuftelin	285	33
114	4105	U32614	Mus musculus SOX6	2855	96
115	4142	X14971	Mus musculus alpha-adaptin (A) (AA 1-977)	4897	98
116	4142	X53773	Rattus norvegicus alpha-c large chain (AA 1-938)	3979	82
117	4149	AF034746	Mus musculus LNXp70	2922	88
118	4196	AC006551	Arabidopsis thaliana Hypothetical protein	214	34

TABLE 2

119	4202	AF229032	Mus musculus piL	2077	93
120	4274	AF056035	Rattus norvegicus s-nexilin	2662	85
121	4304	AK000080	Homo sapiens unnamed protein product	3037	99
122	4306	D88158	Sus scrofa cytochrome b561	474	47
123	4311	AF161445	Homo sapiens HSPC327	1606	100
124	4321	AL133112	Homo sapiens hypothetical protein	1861	100
125	4323	AL137432	Homo sapiens hypothetical protein	3002	100
126	4332	AF186461	Rattus norvegicus ring finger protein Fxy	204	22
127	4488	AE003749	Drosophila melanogaster CG13644 gene product	422	33
128	4588	D87438	Homo sapiens Similar to a C.elegans protein in cosmid C14H10	4069	100
129	5569	D87442	Homo sapiens KIAA0253	3682	100
130	5573	Z15005	Homo sapiens CENP-E	13305	99
131	5577	M59216	Homo sapiens gamma-aminobutyric acid receptor beta-1 subunit	2477	100
132	5579	D31884	Homo sapiens KIAA0063	518	55
133	5582	AF188706	Homo sapiens g20 protein	188	49
134	5583	AB029030	Homo sapiens KIAA1107 protein	6581	99
135	5584	D87446	Homo sapiens Similar to a C.elegans protein encoded in cosmid C27F2 (U40419)	9196	99
136	5585	AF047663	Caenorhabditis elegans W09G12.7 gene product	225	37
137	5591	AC002398	Homo sapiens F25965_1	1018	100
138	5593	AB023215	Homo sapiens KIAA0998 protein	6323	99
139	5594	AF223408	Homo sapiens B99	3686	99
140	5594	AF223408	Homo sapiens B99	2878	88
141	5598	D83781	Homo sapiens the KIAA0197 gene is expressed ubiquitously.; the KIAA0197 protein has histidine acid phosphatase signature at amino acid positions 1047-1061.	6859	99
142	5602	U53450	Rattus norvegicus Jun dimerization protein 1 JDP-1	196	49
143	5605	AL117233	Homo sapiens hypothetical protein	3564	99

TABLE 2

144	5608	U38253	Rattus norvegicus initiation factor eIF-2B gamma subunit	1203	89
145	5617	AE003538	Drosophila melanogaster CG10191 gene product	354	44
146	5620	AB020694	Homo sapiens KIAA0887 protein	2328	100
147	5622	AB029025	Homo sapiens KIAA1102 protein	4394	100
148	5623	AL137255	Homo sapiens hypothetical protein	2636	100
149	5624	AB018289	Homo sapiens KIAA0746 protein	5223	99
150	5625	D38549	Homo sapiens ha1025 is new	6533	99
151	5627	AF241230	Homo sapiens TAK1-binding protein 2	3656	100
152	5628	AK000759	Homo sapiens unnamed protein product	3306	100
153	5630	AL117665	Homo sapiens hypothetical protein	6463	100
154	5632	AF161544	Homo sapiens HSPC059	434	77
155	5640	AJ238248	Homo sapiens centaurin beta2	3986	99
156	5641	AB007929	Homo sapiens KIAA0460 protein	4781	99
157	5643	AF161381	Homo sapiens HSPC263	1404	100
158	5647	AF223468	Homo sapiens AD021 protein	1314	100
159	5649	AF203343	Mus musculus RIBP	115	39
160	5658	X57527	Homo sapiens alpha 1(VIII) collagen	4166	99
161	5659	Y19062	Homo sapiens 39k3 protein	2475	100
162	5667	AK000566	Homo sapiens unnamed protein product	1053	100
163	5672	AL021918	Homo sapiens b34I8.1 (Kruppel related Zinc Finger protein 184)	4184	100
164	5674	AB020706	Homo sapiens KIAA0899 protein	4732	100
165	5678	AB040915	Homo sapiens KIAA1482 protein	2828	99
166	5680	AE001448	Helicobacter pylori J99 THREONINE SYNTHASE	698	37
167	5684	AF226614	Homo sapiens ferroportin1	2929	100
168	5686	Z93241	Homo sapiens dJ222E13.1 (novel protein with some similarity to Drosophila KRAKEN)	513	96
169	5694	AF036977	Homo sapiens unknown	1812	100
170	5698	AK001746	Homo sapiens unnamed	141	45

TABLE 2

			protein product		
171	5699	AF108843	Homo sapiens env protein	320	47
172	5712	AF069781	Drosophila melanogaster Bem46-like protein	653	43
173	5719	U95098	Xenopus laevis mitotic phosphoprotein 44	1200	70
174	5720	X70944	Homo sapiens PTB-associated splicing factor	3883	100
175	5727	AE003741	Drosophila melanogaster CG13832 gene product	456	44
176	5730	AF195833	Mus musculus cell adhesion molecule nectin-3 alpha	2693	93
177	5734	AJ249732	Homo sapiens G8 protein	669	100
178	5738	AF208861	Homo sapiens BM-019	1629	100
179	5739	L09708	Homo sapiens complement component C2	4022	100
180	5740	AF156961	Homo sapiens gag	106	47
181	5744	X66285	Mus musculus HC1 ORF	115	44
182	5748	D00189	Rattus norvegicus Na+,K+-ATPase alpha-subunit	5227	99
183	5749	U10185	Xenopus laevis XPMC2 protein	1020	53
184	5750	AB019038	Homo sapiens beta-1,4 mannosyltransferase	781	77
185	5750	AB019038	Homo sapiens beta-1,4 mannosyltransferase	1347	100
186	5750	AB019038	Homo sapiens beta-1,4 mannosyltransferase	1520	99
187	5761	X84908	Homo sapiens phosphorylase kinase	5729	99
188	5762	X52851	Homo sapiens peptidylprolyl isomerase	650	76
189	5767	AJ245671	Homo sapiens hypothetical protein	3064	100
190	5773	AC004447	Homo sapiens KIAA0365	4963	99
191	5783	U04706	Bos taurus 50 kDa protein	1749	78
192	5784	AF092207	Rattus norvegicus unknown	1180	84
193	5788	AK001934	Homo sapiens unnamed protein product	1368	100
194	5798	AK000284	Homo sapiens unnamed protein product	3385	97
195	5802	AF247042	Homo sapiens tandem pore domain potassium channel TRAAK	2186	99

TABLE 2

196	5807	AF114494	Homo sapiens putative tyrosine phosphatase	1284	99
197	5818	AE000995	Archaeoglobus fulgidus chromosome segregation protein (smc1)	153	20
198	5819	AF062249	Homo sapiens immunoglobulin heavy chain variable region	605	97
199	5827	AJ223830	Rattus norvegicus ARE1	2950	98
200	5828	AL133027	Homo sapiens hypothetical protein	1224	84
201	5842	D87684	Homo sapiens KIAA0242 protein	2566	100
202	5853	AL050318	Homo sapiens dJ977B1.3.1 (novel protein similar to putative RAB5-interacting protein (isoform 1))	524	79
203	5861	D49387	Homo sapiens NADP dependent leukotriene b4 12-hydroxydehydrogenase	1616	100
204	5864	AL050022	Homo sapiens hypothetical protein	330	34
205	5865	AL050267	Homo sapiens hypothetical protein	3325	99
206	5871	AL137300	Homo sapiens hypothetical protein	1056	98
207	5873	AK001480	Homo sapiens unnamed protein product	1562	99
208	5873	AK001480	Homo sapiens unnamed protein product	1082	98
209	5875	X12966	Homo sapiens 3-oxoacyl-CoA thiolase propeptide (424 AA)	1972	100
210	5878	Y09267	Homo sapiens flavin-containing monooxygenase 2	2486	100
211	5879	Z11773	Homo sapiens SRE-ZBP	2201	99
212	5880	D84224	Homo sapiens methionyl tRNA synthetase	4741	99
213	5880	D84224	Homo sapiens methionyl tRNA synthetase	3887	99
214	5880	D84224	Homo sapiens methionyl tRNA synthetase	2933	96
215	5880	D84224	Homo sapiens methionyl tRNA synthetase	4529	99
216	5885	J03244	Bos taurus H+ ATPase 31kDa subunit (EC 3.6.1.3)	848	77
217	5895	AK001589	Homo sapiens unnamed protein product	2313	100
218	5898	AL117615	Homo sapiens hypothetical protein	3174	99
219	5902	AE003735	Drosophila	436	58

TABLE 2

			melanogaster CG6353 gene product		
220	5904	A06669	synthetic construct preTGF-beta1	2070	99
221	5918	AE003487	Drosophila melanogaster CG1905 gene product	238	26
222	5921	AL110243	Homo sapiens hypothetical protein	2275	100
223	5927	X60271	Mus musculus c-rel	2264	74
224	5932	AK001475	Homo sapiens unnamed protein product	3025	100
225	5939	AF131851	Homo sapiens Unknown	262	44
226	5945	AB002320	Homo sapiens KIAA0322	8183	100
227	5946	AE003518	Drosophila melanogaster CG6836 gene product	135	22
228	5947	AF119855	Homo sapiens PRO1847	265	67
229	5956	M17236	Homo sapiens MHC HLA-DQ alpha precursor	1332	100
230	5967	AK001345	Homo sapiens unnamed protein product	1453	99
231	5968	M28515	Mus musculus zinc finger protein mfg3 mRNA (put.); putative	225	28
232	5975	AB037730	Homo sapiens KIAA1309 protein	515	44
233	5977	AE003464	Drosophila melanogaster CG11414 gene product	610	44
234	5978	M12140	Homo sapiens pol gene protein; Xxx	117	50
235	5979	U79267	Homo sapiens unknown	225	56
236	5980	X56681	Homo sapiens junD protein	373	88
237	5988	AB023151	Homo sapiens KIAA0934 protein	7099	100
238	5989	AL109839	Homo sapiens dJ1069P2.3.1 (novel PABPC1 (poly(A)-binding protein, cytoplasmic 1) (PABPL1) like protein (putative isoform 1))	877	100
239	5991	AE003583	Drosophila melanogaster BcDNA:GH09817 gene product	289	42
240	5997	AF052723	Feline leukemia virus gag-pol precursor polyprotein gPr80	1547	44
241	5998	AF161472	Homo sapiens HSPC123	439	45
242	6003	AK000360	Homo sapiens unnamed protein product	796	100
243	6004	U09848	Homo sapiens zinc finger protein	1738	100

TABLE 2

244	6013	U19177	Homo sapiens Hin-2	55	46
245	6028	AF155113	Homo sapiens NY-REN-55 antigen	3603	93
246	6028	AF155113	Homo sapiens NY-REN-55 antigen	3951	99
247	6029	AL032821	Homo sapiens dJ55C23.1 (vanin 1)	1821	98
248	6031	M69181	Homo sapiens non-muscle myosin B	7350	99
249	6031	M69181	Homo sapiens non-muscle myosin B	7311	98
250	6032	X61280	Oryza sativa hydroxyproline-rich glycoprotein	143	38
251	6037	AB002330	Homo sapiens KIAA0332	5362	100
252	6037	AB002330	Homo sapiens KIAA0332	4897	97
253	6043	X06745	Homo sapiens DNA polymerase alpha-subunit (AA 1 - 1462)	7619	99
254	6044	AF252292	Homo sapiens PAR6C	1342	100
255	6046	D86984	Homo sapiens similar to yeast adenylate cyclase (S56776)	2446	100
256	6048	AF165124	Homo sapiens gamma-aminobutyric acid A receptor gamma 2	2499	99
257	6049	AF110267	Rattus norvegicus golgi stacking protein homolog GRASP55	2088	89
258	6051	U82319	Homo sapiens novel ORF	342	100
259	6053	Y00816	Homo sapiens CR1 precursor protein	11396	99
260	6060	AJ223948	Homo sapiens RNA helicase	6608	99
261	6063	Y08612	Homo sapiens 88kDa nuclear pore complex protein	3874	99
262	6066	AB014597	Homo sapiens KIAA0697 protein	5060	100
263	6067	AF129756	Homo sapiens BAT4	1873	98
264	6068	AF131775	Homo sapiens Unknown	1929	99
265	6073	AJ250865	Homo sapiens TESS 2	2348	100
266	6076	Z98885	Homo sapiens dJ522J7.2 (bromodomain-containing 1 (similar to peregrin, BR140))	5588	100
267	6076	Z98885	Homo sapiens dJ522J7.2 (bromodomain-containing 1 (similar to peregrin, BR140))	4167	100
268	6077	L76571	Homo sapiens nuclear hormone receptor	1355	100
269	6079	AF091622	Homo sapiens PHD finger protein 3	9054	100
270	6082	X56807	Homo sapiens	4443	100

TABLE 2

			desmocollin type 2a		
271	6087	AC002464	Homo sapiens organic cation transporter; 50% similarity to JC4884 (PID:g2143892)	1542	99
272	6088	AL050272	Homo sapiens hypothetical protein	697	99
273	6091	AL022329	Homo sapiens bK407F11.2 (adrenergic, beta, receptor kinase 2)	3653	100
274	6094	AK000833	Homo sapiens unnamed protein product	2001	98
275	6101	AJ245600	Homo sapiens hypothetical protein	2616	99
276	6103	AB041810	Mus musculus unnamed protein product	1468	91
277	6104	L36531	Homo sapiens integrin alpha 8 subunit	5386	99
278	6108	AL117646	Homo sapiens hypothetical protein	1491	100
279	6112	AF218584	Homo sapiens GGA1	3265	100
280	6121	Y13115	Homo sapiens serine/threonine protein kinase	5071	99
281	6125	AB018319	Homo sapiens KIAA0776 protein	3960	99
282	6126	AL034452	Homo sapiens dJ682J15.1 (novel Collagen triple helix repeat containing protein)	1979	100
283	6128	Y14494	Homo sapiens aralar1	3465	99
284	6129	AJ001981	Homo sapiens OXA1L	2603	100
285	6133	A58799	unidentified unnamed protein product	3069	100
286	6133	A58799	unidentified unnamed protein product	2464	100
287	6135	AF163572	Homo sapiens Forssman glycolipid synthetase	1865	99
288	6139	AF161503	Homo sapiens HSPC154	1261	97
289	6141	AB011125	Homo sapiens KIAA0553 protein	5754	100
290	6145	AJ250014	Homo sapiens Familial Cylindromatosis Gene	3655	99
291	6146	D25217	Homo sapiens KIAA0027 protein	361	94
292	6148	X85786	Homo sapiens binding regulatory factor	3203	100
293	6149	Y08319	Homo sapiens kinesin-2	3487	99
294	6149	D12644	Mus musculus KIF2 protein	3609	97
295	6153	U28789	Mus musculus PACT	5936	89
296	6159	AL137515	Homo sapiens hypothetical protein	1687	100

TABLE 2

297	6164	AB020705	Homo sapiens KIAA0898 protein	5017	100
298	6167	Y00062	Homo sapiens precursor polypeptide (AA -23 to 1120)	3440	99
299	6172	AB007941	Homo sapiens KIAA0472 protein	1925	99
300	6173	X98248	Homo sapiens sortilin	4403	99
301	6190	X61100	Homo sapiens 75 kDa subunit NADH dehydrogenase precursor	3734	99
302	6194	S58544	Homo sapiens 75 kda infertility-related sperm protein	2125	99
303	6196	AL110265	Homo sapiens hypothetical protein	744	100
304	6197	X14968	Homo sapiens RII-alpha subunit (AA 1-404)	2079	100
305	6198	AL050283	Homo sapiens hypothetical protein	1983	100
306	6198	AL050283	Homo sapiens hypothetical protein	1694	100
307	6205	AJ011863	Homo sapiens homeobox protein LSX	3841	99
308	6214	AF098786	Homo sapiens 17 beta-hydroxysteroid dehydrogenase type VII	1754	100
309	6215	AL034555	Homo sapiens dJ134O19.3 (zinc finger protein 151 (pHZ-67))	4273	100
310	6219	AB011167	Homo sapiens KIAA0595 protein	7678	98
311	6226	U39205	Saccharomyces cerevisiae Lpe10p	277	29
312	6229	AF041429	Homo sapiens pRGR1	823	99
313	6234	X66357	Homo sapiens serine/threonine protein kinase	1589	100
314	6237	Y11284	Homo sapiens AFX1	2571	98
315	6238	AB004884	Homo sapiens PKU-alpha	3718	99
316	6239	AJ002303	Homo sapiens synaptogyrin 1c	1020	100
317	6239	AJ002304	Homo sapiens synaptogyrin 1b	1002	100
318	6239	AJ002303	Homo sapiens synaptogyrin 1c	933	94
319	6240	D87682	Homo sapiens similar to a C.elegans protein encoded in cosmid T26A5.	2676	100
320	6244	M14660	Homo sapiens ISG-K54	2473	99
321	6245	X06661	Homo sapiens calbindin (AA 1-261)	1358	100
322	6250	AF119900	Homo sapiens PRO2822	185	76

TABLE 2

323	6252	AB014527	Homo sapiens KIAA0627 protein	6478	99
324	6252	AB014527	Homo sapiens KIAA0627 protein	6372	98
325	6256	X86691	Homo sapiens Mi-2 protein	10110	99
326	6260	AE003628	Drosophila melanogaster CG7475 gene product	985	57
327	6261	AF236061	Oryctolagus cuniculus RING-finger binding protein	3830	91
328	6264	AB018327	Homo sapiens KIAA0784 protein	5708	100
329	6265	AB018314	Homo sapiens KIAA0771 protein	4949	100
330	6266	AB002318	Homo sapiens KIAA0320	4639	99
331	6270	X14766	Homo sapiens GABA-A receptor alpha 1 subunit	2388	99
332	6271	AB023177	Homo sapiens KIAA0960 protein	7294	99
333	6272	AB032957	Homo sapiens KIAA1131 protein	8443	100
334	6274	AF007155	Homo sapiens unknown	187	61
335	6276	Z34975	Homo sapiens ldlCp	3733	100
336	6281	AL050306	Homo sapiens dJ475B7.2 (novel protein)	3796	100
337	6281	AL050306	Homo sapiens dJ475B7.2 (novel protein)	1942	99
338	6288	AB014566	Homo sapiens KIAA0666 protein	5541	100
339	6292	AB018353	Homo sapiens KIAA0810 protein	4246	100
340	6294	Z21966	Homo sapiens mPOU homeobox protein	1529	100
341	6299	AL022395	Homo sapiens dJ273N12.1 (PUTATIVE protein based on EST matches)	3287	100
342	6299	AL022395	Homo sapiens dJ273N12.1 (PUTATIVE protein based on EST matches)	2403	83
343	6312	AL096713	Homo sapiens hypothetical protein	7599	99
344	6312	AF182316	Homo sapiens myoferlin	6232	99
345	6312	AL096713	Homo sapiens hypothetical protein	6120	99
346	6322	AK000218	Homo sapiens unnamed protein product	1163	99
347	6324	D42046	Homo sapiens The ha3631 gene product is related to S.cerevisiae protein encoded in chromosome	5568	100

TABLE 2

			VIII.		
348	6328	AB023624	Rattus norvegicus SCOP	4792	92
349	6329	X59303	Homo sapiens valyl-tRNA synthetase	3393	99
350	6331	AC004142	Homo sapiens similar to murine leucine-rich repeat protein; possible role in neural development by protein-protein interactions; 93% similarity to D49802 (PID:g1369906)	3676	100
351	6333	AC009991	Arabidopsis thaliana unknown protein	609	51
352	6334	AB018271	Homo sapiens KIAA0728 protein	4316	98
353	6337	AB002318	Homo sapiens KIAA0320	4639	99
354	6339	AB039371	Homo sapiens mitochondrial ABC transporter 3	2902	99
355	6346	AK002198	Homo sapiens unnamed protein product	2570	99
356	6348	AB033087	Homo sapiens KIAA1261 protein	4094	99
357	6348	L14463	Rattus norvegicus 'transducin	3619	92
358	6350	AC005757	Homo sapiens R32611_1	2779	100
359	6351	S61069	Homo sapiens reverse transcriptase homolog=pol {retroviral element}	252	66
360	6355	AF271388	Homo sapiens CMP-N-acetylneuraminic acid synthase	2273	100
361	6362	X79066	Homo sapiens ERF-1	1783	100
362	6368	AF118566	Mus musculus hematopoietic zinc finger protein	769	51
363	6369	AB020710	Homo sapiens KIAA0903 protein	4915	99
364	6371	AF143321	Homo sapiens unknown	661	65
365	6376	AF260011	Homo sapiens HSPC087-KIAA0714	8764	99
366	6379	S83365	Homo sapiens putative Rab5-interacting protein {clone L1-94}	131	49
367	6380	AL021878	Homo sapiens dJ257I20.4 (transcription factor 20 (AR1) (KIAA0292) (isoform 2))	154	68
368	6381	D90734	Escherichia coli ORF_ID:o223#11	628	100
369	6392	M58378	Homo sapiens synapsin I	3730	99

TABLE 2

370	6395	AF039697	Homo sapiens antigen NY-CO-31	508	98
371	6397	U09355	Oryctolagus cuniculus protein phosphatase 2A1 B gamma subunit	2356	99
372	6400	AB002293	Homo sapiens KIAA0295	5054	100
373	6401	AC004774	Homo sapiens Dlx-5	1542	100
374	6411	X90530	Homo sapiens ragB	1926	99
375	6411	X90530	Homo sapiens ragB	1405	99
376	6411	X90530	Homo sapiens ragB	1590	85
377	6416	AL080157	Homo sapiens hypothetical protein	2100	94
378	6418	AE003628	Drosophila melanogaster CG5188 gene product	659	49
379	6422	AB007884	Homo sapiens KIAA0424	2757	99
380	6423	AB018323	Homo sapiens KIAA0780 protein	5631	100
381	6426	AF042713	Rattus norvegicus neurexophilin 3	1337	96
382	6427	AJ131891	Homo sapiens DNA polymerase mu	1451	100
383	6428	AF221712	Homo sapiens Smad- and Olf-interacting zinc finger protein	6705	100
384	6429	X83573	Homo sapiens ARSE	3184	99
385	6430	AJ243274	Homo sapiens AP-2rep protein	2078	99
386	6432	AL035608	Homo sapiens dJ479J7.1 (similar to CHONDROMODULIN-1)	1440	100
387	6432	AL035608	Homo sapiens dJ479J7.1 (similar to CHONDROMODULIN-1)	1316	93
388	6438	AK001444	Homo sapiens unnamed protein product	943	100
389	6441	AL022237	Homo sapiens bK1191B2.3 (PUTATIVE novel Acyl Transferase similar to C. elegans C50D2.7) (isoform 1))	2030	100
390	6446	AJ006266	Homo sapiens AND-1 protein	5942	100
391	6454	AL110240	Homo sapiens hypothetical protein	704	98
392	6459	AL050149	Homo sapiens hypothetical protein	2899	100
393	6460	AL096772	Homo sapiens dJ365O12.1 (KIAA0758 protein)	7049	99
394	6461	AB008376	Sus scrofa 17-kDa PKC-potentiated inhibitory protein of PP1	689	91
395	6467	M22334	Homo sapiens unknown protein	796	59

TABLE 2

396	6468	AK002144	Homo sapiens unnamed protein product	2719	100
397	6487	AL117429	Homo sapiens hypothetical protein	1077	100
398	6491	AB027004	Homo sapiens protein phosphatase	435	48
399	6506	AL137013	Homo sapiens bA311P8.3 (probable uracil phosphoribosyltranferase)	862	100
400	6513	AL080141	Homo sapiens hypothetical protein	4793	99
401	6514	AB035123	Mus musculus GD1 alpha/GT1a alpha/GQ1b alpha synthase	1696	93
402	6519	K02882	Homo sapiens immunoglobulin delta-chain	2048	100
403	6521	X07979	Homo sapiens integrin beta 1 subunit precursor	4347	99
404	6532	AJ224819	Homo sapiens tumor suppressor	2149	99
405	6536	Y07595	Homo sapiens transcription factor TFIIH	2373	100
406	6543	D14479	Rattus norvegicus calpain	1428	88
407	6544	AF161341	Homo sapiens HSPC078	1097	98
408	6548	AF187318	Homo sapiens F-box protein Fbx2	1607	100
409	6551	AL050369	Homo sapiens hypothetical protein	2495	99
410	6551	AL050369	Homo sapiens hypothetical protein	2135	99
411	6552	AE003785	Drosophila melanogaster CG12792 gene product	1211	56
412	6554	AF091083	Homo sapiens unknown	1514	100
413	6556	AK001708	Homo sapiens unnamed protein product	2334	99
414	6560	AE003602	Drosophila melanogaster CG2109 gene product	462	38
415	6563	AB011139	Homo sapiens KIAA0567 protein	4966	99
416	6564	AK001177	Homo sapiens unnamed protein product	1933	100
417	6567	D63484	Homo sapiens The KIAA0150 gene product is novel.	4951	99
418	6573	AB029012	Homo sapiens KIAA1089 protein	5128	100
419	6575	AL035461	Homo sapiens dJ967N21.6 (novel CDP-alcohol	1562	98

TABLE 2

			phosphatidyltransferase family member protein)		
420	6577	AK001236	Homo sapiens unnamed protein product	1676	99
421	6593	AF079098	Homo sapiens arginine-tRNA-protein transferase 1-1p; ATE1-1p	2733	99
422	6595	AJ131712	Homo sapiens nucleolar RNA-helicase	2793	100
423	6599	AJ133115	Homo sapiens TSC-22-like protein	2054	99
424	6625	X98258	Homo sapiens M-phase phosphoprotein 9	953	100
425	6625	X98258	Homo sapiens M-phase phosphoprotein 9	564	75
426	6626	U97191	Caenorhabditis elegans strong similarity to the YPT1 sub-family of RAS proteins	960	85
427	6630	X76057	Homo sapiens phosphomannose isomerase	2191	100
428	6631	AE003559	Drosophila melanogaster CG8605 gene product	650	31
429	6632	X97064	Homo sapiens Sec23 protein	4034	99
430	6633	AF161401	Homo sapiens HSPC283	779	100
431	6634	AJ005642	Rattus rattus serine protease	717	48
432	6638	M19529	Sus scrofa follistatin A	1906	98
433	6641	AJ249457	Trichomonas vaginalis centrin, putative	183	28
434	6644	AC004410	Homo sapiens fos39554_1	2094	100
435	6646	AK000096	Homo sapiens unnamed protein product	2157	99
436	6648	AF252284	Homo sapiens transcription specificity factor Sp1	4005	100
437	6652	Z92825	Caenorhabditis elegans predicted using Genefinder~cDNA EST yk315e12.3 comes from this gene~cDNA EST yk315e12.5 comes from this gene~cDNA EST yk605b12.3 comes from this gene	541	43
438	6654	D79205	Homo sapiens ribosomal protein L39	160	77
439	6657	AL031027	Unknown /prediction=(method:""	584	58

TABLE 2

			genefinder"", version:""084"", score:""67.72"")~/prediction=(method		
440	6658	S49657	Mus sp. mitochondrial capsule selenoprotein; MCS	91	35
441	6663	M26312	Oryctolagus cuniculus unknown protein	82	30
442	6664	L32162	Homo sapiens transcription factor	574	80
443	6668	AL050060	Homo sapiens hypothetical protein	526	99
444	6669	AF205936	Mus musculus ADP-ribosylation factor-like membrane-associated protein	296	39
445	6673	AK000387	Homo sapiens unnamed protein product	1136	100
446	6685	U38934	Gallus gallus histone H2A	625	97
447	6687	U76374	Mus musculus skm-BOP2	602	31
448	6689	X13403	Homo sapiens Oct-1 protein (AA 1 - 743)	3626	100
449	6693	AB023139	Homo sapiens KIAA0922 protein	4258	100
450	6698	AE003467	Drosophila melanogaster CG7047 gene product	274	27
451	6699	AL049176	Homo sapiens dA141H5.1 (C-terminal part of a Chordin LIKE protein with von Willebrand factor type C domains)	1401	99
452	6705	X92475	Homo sapiens ITBA1	1429	100
453	6711	Y16752	Homo sapiens secretagogin	1422	99
454	6713	X51416	Homo sapiens hormone receptor hERR1 (AA 1-521)	2641	97
455	6716	AJ006591	Homo sapiens cysteine-rich protein	1793	100
456	6725	A08695	Homo sapiens rap2	935	100
457	6726	Z12173	Homo sapiens N-acetylglucosamine-6-sulphatase	2970	100
458	6727	AL355092	Homo sapiens hypothetical protein	924	98
459	6730	AB007930	Homo sapiens KIAA0461 perotein	7164	100
460	6730	AB007930	Homo sapiens KIAA0461 perotein	6960	99
461	6730	AB007930	Homo sapiens KIAA0461 perotein	6018	89
462	6732	D38491	Homo sapiens KIAA0117	1119	99
463	6733	AJ012590	Homo sapiens glucose	4155	99

TABLE 2

			1-dehydrogenase		
464	6737	AL080133	Homo sapiens hypothetical protein	5677	100
465	6745	Z75532	Caenorhabditis elegans similar to mitochrondrial carrier protein-cDNA EST yk264h5.5 comes from this gene	220	35
466	6751	AF207829	Homo sapiens SCAN-related protein RAZ1	900	100
467	6754	AF061262	Mus musculus semaF cytoplasmic domain associated protein 2	1316	83
468	6758	AF220189	Homo sapiens uncharacterized hypothalamus protein HBEX2	605	89
469	6761	AL079292	Homo sapiens hypothetical protein, similar to (AC007017) putative RNA helicase A	4135	100
470	6765	Z22819	Mus musculus Rab24 protein	1042	98
471	6768	Z97029	Homo sapiens ribonuclease HI large subunit	1548	99
472	6773	AB035384	Homo sapiens SRp25 nuclear protein	962	94
473	6776	AF024631	Homo sapiens ANG2	2644	100
474	6796	AJ006710	Rattus norvegicus phosphatidylinositol 3-kinase	4508	97
475	6798	AL137275	Homo sapiens hypothetical protein	4310	100
476	6823	V00638	bacteriophage lambda reading frame ea10	600	100
477	6825	AF049103	Homo sapiens Huntingtin interacting protein	819	100
478	6826	U50312	Caenorhabditis elegans strong similarity to the a portion of the triple-helical region of collagen alpha chain	92	40
479	6839	Z26317	Homo sapiens desmoglein 2	4810	99
480	6844	AF227899	Homo sapiens breast carcinoma-associated antigen isoform I	4443	99
481	6847	AF106037	Homo sapiens adipocyte-derived leucine aminopeptidase	4905	99
482	6849	U15155	Gallus gallus	372	37

TABLE 2

			trypsinogen		
483	6854	D86974	Homo sapiens KIAA0220	2870	99
484	6857	AF112201	Homo sapiens neuronal protein NP25	1053	100
485	6861	AF234765	Rattus norvegicus serine-arginine-rich splicing regulatory protein SRRP86	958	64
486	6873	AF117383	Homo sapiens placental protein 13; PP13	502	68
487	6875	AK002059	Homo sapiens unnamed protein product	1665	100
488	6877	AE003438	Drosophila melanogaster CG3184 gene product	338	43
489	6880	AK000101	Homo sapiens unnamed protein product	814	100
490	6885	AK000609	Homo sapiens unnamed protein product	1160	100
491	6890	AB023201	Homo sapiens KIAA0984 protein	3743	98
492	6890	AB023201	Homo sapiens KIAA0984 protein	2361	97
493	6894	AB013885	Homo sapiens beta-ureidopropionase	1494	100
494	6901	AL096725	Homo sapiens hypothetical protein	1901	100
495	6904	AK001901	Homo sapiens unnamed protein product	2212	99
496	6907	AF226077	Homo sapiens CHRAC17	724	99
497	6914	AE003762	Drosophila melanogaster CG5590 gene product	646	75
498	6917	Z73497	Homo sapiens cU240C2.2 (Core histone H2A/H2B/H3/H4)	324	100
499	6923	Z83246	Caenorhabditis elegans predicted using Genefinder~cDNA EST EMBL:M79771 comes from this gene	891	60
500	6929	X16282	Homo sapiens zinc finger protein (217 AA) (1 is 2nd base in codon)	1109	99
501	6931	Z92539	Mycobacterium tuberculosis pth	300	36
502	6935	M62324	Homo sapiens modulator recognition factor I	2902	96
503	6940	AC024762	Caenorhabditis elegans Hypothetical protein Y38F2AL.f	434	43
504	6945	AL117555	Homo sapiens hypothetical protein	321	94
505	6946	AC005328	Homo sapiens R26660_2, partial CDS	865	97

TABLE 2

506	6947	AF151075	Homo sapiens HSPC241	686	98
507	6949	L34807	Musca domestica transposase	174	21
508	6959	AJ271091	Homo sapiens B-ind1 protein	494	42
509	6960	AK001348	Homo sapiens unnamed protein product	1853	99
510	6962	AJ006692	Homo sapiens ultra high sulfer keratin	693	74
511	6963	U23037	Oryctolagus cuniculus eIF-2Bepsilon	3406	90
512	6967	AL136571	Homo sapiens hypothetical protein	413	58
513	6983	AF151800	Homo sapiens CGI-41 protein	84	35
514	6988	AF198100	Fowlpox virus ORF FPV114 HAL3 domain	567	54
515	6996	AL137764	Homo sapiens hypothetical protein	2162	100
516	7003	AB011792	Homo sapiens extracellular matrix protein	274	35
517	7016	AB011542	Homo sapiens MEGF9	2097	100
518	7017	AL096744	Homo sapiens hypothetical protein	231	68
519	7025	AF119664	Homo sapiens transcriptional regulator protein HCNGP	1574	100
520	7025	AF119664	Homo sapiens transcriptional regulator protein HCNGP	1144	89
521	7025	AF119664	Homo sapiens transcriptional regulator protein HCNGP	1448	94
522	7050	X12517	Homo sapiens C protein (AA 1-159)	918	100
523	7051	AL079277	Homo sapiens hypothetical protein, similar to (U32865) linotte protein	1294	100
524	7055	AF067730	Homo sapiens TLS-associated protein TASR-2	631	57
525	7060	U27831	Homo sapiens striatum-enriched phosphatase	2840	98
526	7064	L26288	Rattus norvegicus CaM-like protein kinase	1416	82
527	7067	AL032684	Schizosaccharomyces pombe hypothetical protein	300	37
528	7071	AL050028	Homo sapiens hypothetical protein	671	100
529	7072	X78444	Rattus norvegicus	450	73

TABLE 2

			ribosomal protein L22		
530	7073	U27838	Mus musculus glycosyl-phosphatidyl-inositol-anchored protein homolog	3305	96
531	7076	AB037807	Homo sapiens KIAA1386 protein	4001	99
532	7088	AJ276504	Mus musculus phosphorylated adaptor for RNA export	1705	85
533	7089	AB033079	Homo sapiens KIAA1253 protein	2398	100
534	7091	U41315	Homo sapiens ZNF127-Xp	2458	93
535	7091	AF192784	Homo sapiens makorin 1	2062	97
536	7104	AE003704	Drosophila melanogaster CG3307 gene product	510	44
537	7105	Z22968	Homo sapiens M130 antigen	6205	100
538	7105	Z22971	Homo sapiens M130 antigen extracellular variant	6380	100
539	7109	AL050225	Homo sapiens hypothetical protein	1431	99
540	7109	AL050225	Homo sapiens hypothetical protein	932	99
541	7119	Z46522	Drosophila subobscura bcn92	237	55
542	7120	AE003771	Drosophila melanogaster CG1972 gene product	2185	68
543	7121	AL021546	Homo sapiens Cytochrome C Oxidase Polypeptide VIa-liver precursor (EC 1.9.3.1)	593	100
544	7126	L02956	Xenopus laevis ribonucleoprotein	1664	87
545	7127	AF201947	Homo sapiens MEK binding partner 1	616	100
546	7130	L31783	Mus musculus uridine kinase	1266	92
547	7131	AK001534	Homo sapiens unnamed protein product	652	97
548	7144	AE003834	Drosophila melanogaster CG8026 gene product	485	57
549	7159	AF154108	Homo sapiens tumor necrosis factor type 1 receptor associated protein	3559	99
550	7163	AE003066	Drosophila melanogaster CG13865 gene product	251	34
551	7175	X57807	Homo sapiens immunoglobulin lambda light chain	699	91

TABLE 2

552	7188	AL031673	Homo sapiens dJ694B14.1 (PUTATIVE novel KRAB box protein with 18 C2H2 type Zinc finger domains)	4066	99
553	7189	Y11652	Homo sapiens phosphate cyclase	238	100
554	7190	AF192968	Homo sapiens high-glucose-regulated protein 8	3041	99
555	7191	AB020648	Homo sapiens KIAA0841 protein	3237	99
556	7203	AL031427	Homo sapiens dJ167A19.1 (novel protein)	1608	100
557	7204	AF151534	Homo sapiens core histone macroH2A2.2	1866	100
558	7208	AL021331	Homo sapiens dJ366N23.1 (putative C. elegans UNC-93 (protein 1, C46F11.1) LIKE protein)	1129	100
559	7209	X14608	Homo sapiens propionyl-CoA carboxylase	3579	100
560	7210	AL110249	Homo sapiens hypothetical protein	4488	99
561	7216	AC004982	Homo sapiens similar to yeast hypothetical protein ybk4; similar to P38164 (PID:g586461)	2038	100
562	7221	AE003628	Drosophila melanogaster CG5676 gene product	148	30
563	7230	AE003519	Drosophila melanogaster CG4108 gene product	711	75
564	7237	X79417	Sus scrofa 40S ribosomal protein S12	687	100
565	7240	AB023203	Homo sapiens KIAA0986 protein	7551	100
566	7245	AE003684	Drosophila melanogaster CG8412 gene product	1106	51
567	7250	AL117662	Homo sapiens hypothetical protein	1078	99
568	7251	AB041261	Homo sapiens calcium-independent phospholipase A2	2903	100
569	7255	AK000812	Homo sapiens unnamed protein product	1350	100
570	7260	Y10936	Homo sapiens hypothetical protein	1104	99
571	7265	AK000444	Homo sapiens unnamed protein product	2900	99

TABLE 2

572	7268	AK001798	Homo sapiens unnamed protein product	1460	99
573	7275	AL117635	Homo sapiens hypothetical protein	929	99
574	7279	M55531	Homo sapiens GLUT5 protein	924	45
575	7283	AL117573	Homo sapiens hypothetical protein	2907	99
576	7283	AL117573	Homo sapiens hypothetical protein	2457	97
577	7287	AF237631	Homo sapiens ubiquitous tropomodulin U-Tmod	1798	100
578	7301	AF090929	Homo sapiens PRO0477p	653	99
579	7308	AL031228	Homo sapiens dJ1033B10.2 (WD40 protein BING4 (similar to S. cerevisiae YER082C, M. sexta MNG10 and C. elegans F28D1.1)	3196	100
580	7308	AL031228	Homo sapiens dJ1033B10.2 (WD40 protein BING4 (similar to S. cerevisiae YER082C, M. sexta MNG10 and C. elegans F28D1.1)	2825	96
581	7309	AF171102	Homo sapiens retinal degeneration B beta	1302	95
582	7319	AK001598	Homo sapiens unnamed protein product	2775	100
583	7320	AJ237946	Homo sapiens DEAD Box Protein 5	2443	100
584	7326	Z97184	Homo sapiens HKE2	624	100
585	7326	Z97184	Homo sapiens HKE2	409	98
586	7334	AJ245587	Homo sapiens Kruppel-type zinc finger	1942	100
587	7337	Z22820	Canis familiaris Rab22a protein	995	98
588	7339	X64701	Haloferax mediterranei gvpI	103	28
589	7344	L04733	Homo sapiens kinesin light chain	1936	72
590	7355	AB020681	Homo sapiens KIAA0874 protein	3090	100
591	7363	M55542	Homo sapiens guanylate binding protein isoform I	2993	98
592	7363	M55542	Homo sapiens guanylate binding protein isoform I	2901	96
593	7365	U41857	Xenopus laevis WD-40 motifs; up-regulated by thyroid hormone in tadpoles	937	53

TABLE 2

594	7368	M26285	Xenopus laevis myc protein	82	28
595	7369	AB029150	Homo sapiens KRAB zinc finger protein HFB101L	2196	100
596	7372	AK000706	Homo sapiens unnamed protein product	1641	100
597	7373	AB041648	Mus musculus unnamed protein product	625	100
598	7374	AB032976	Homo sapiens KIAA1150 protein	1929	100
599	7375	AB011182	Homo sapiens KIAA0610 protein	3467	100
600	7381	AJ243721	Homo sapiens dTDP-4-keto-6-deoxy-D-glucose 4-reductase	1710	100
601	7383	Z46676	Caenorhabditis elegans cDNA EST yk484g1.3 comes from this gene-cDNA EST yk484g1.5 comes from this gene	312	40
602	7387	L24804	Homo sapiens p23	350	43
603	7391	AK000453	Homo sapiens unnamed protein product	1843	99
604	7393	D50807	Bos taurus synaphin	146	35
605	7395	M23159	Cricetus cricetus DHFR-coamplified protein	163	31
606	7397	AB020684	Homo sapiens KIAA0877 protein	3034	100
607	7399	AK002205	Homo sapiens unnamed protein product	1331	97
608	7405	AL096779	Homo sapiens hypothetical protein	1544	100
609	7406	AL161495	Arabidopsis thaliana putative WD-repeat protein	866	43
610	7406	AL161495	Arabidopsis thaliana putative WD-repeat protein	442	36
611	7409	U97001	Caenorhabditis elegans similar to Schizosaccharomyces pombe 4-nitrophenylphosphatase (PNPPASE) (GB:X62722, NID:g5005)	605	52
612	7410	X71978	Mus musculus Fif	1503	95
613	7411	AL117526	Homo sapiens hypothetical protein	4375	99
614	7417	AL031765	Unknown /prediction=(method:"" genefinder"", version:""084"", score:""31.96"")~/prediction=(method	364	35

TABLE 2

615	7418	AK001743	Homo sapiens unnamed protein product	2248	99
616	7421	AE003557	Drosophila melanogaster CG7388 gene product	471	39
617	7422	AJ224326	Homo sapiens ribulose-5-phosphate-epimerase	912	100
618	7422	AE003840	Drosophila melanogaster CG1364 gene product	363	60
619	7423	AB023191	Homo sapiens KIAA0974 protein	2953	100
620	7424	AE003750	Drosophila melanogaster CG11839 gene product	201	31
621	7426	AJ276485	Homo sapiens integral membrane transporter protein	1200	100
622	7427	AK000062	Homo sapiens unnamed protein product	1390	63
623	7428	AB026808	Mus musculus synaptotagmin XI	2142	95
624	7430	AB015345	Homo sapiens HRIHFB2216	2601	99
625	7435	X65724	Homo sapiens ORF2	498	100
626	7437	AE003474	Drosophila melanogaster CG1275 gene product	489	43
627	7439	AK002204	Homo sapiens unnamed protein product	1138	100
628	7440	AK001675	Homo sapiens unnamed protein product	1289	100
629	7442	AC006978	Homo sapiens supported by human and rodent ESTs; match to AA454028 (NID:g2167697), similar to AA9255224 (NID:g4236415) and AA023712 (NID:g1487627)	501	100
630	7450	AF129756	Homo sapiens G5c	273	100
631	7451	M23765	Rattus norvegicus alpha-tropomyosin	133	96
632	7452	Z80220	Caenorhabditis elegans Similarity to yeast protein TREMBL ID E246895)~cDNA EST EMBL:T00018 comes from this gene~cDNA EST EMBL:C13908 comes from this gene~cDNA EST EMBL:C11656 comes from this gene~cDNA EST yk234a5.3 comes from this gene~cDNA EST	601	57

TABLE 2

			yk234a5.5 comes from this gene~cDNA EST yk590h6.3 comes from this gene		
633	7454	AL117530	Homo sapiens hypothetical protein	2121	99
634	7457	AF055473	Homo sapiens GAGE-8	273	52
635	7459	AL050147	Homo sapiens hypothetical protein	2847	100
636	7461	AF143956	Mus musculus coronin-2	2300	93
637	7463	AK002072	Homo sapiens unnamed protein product	1858	98
638	7466	AF060076	Mus musculus polyhomeotic 2 protein	147	45
639	7469	Z98944	Schizosaccharomyces pombe hypothetical protein	159	44
640	7473	U66208	Ascaris suum AsSLR8.60	128	54
641	7481	AK000337	Homo sapiens unnamed protein product	1319	62
642	7482	U09410	Homo sapiens zinc finger protein ZNF131	2483	99
643	7482	U09410	Homo sapiens zinc finger protein ZNF131	1853	99
644	7483	AF068302	Homo sapiens choline/ethanolamineph osphotransferase	1356	66
645	7485	AK000427	Homo sapiens unnamed protein product	1140	100
646	7486	U54807	Rattus norvegicus GTP-binding protein	1167	97
647	7487	AF058807	Bos taurus GTP-binding protein rah	606	97
648	7491	AL050269	Homo sapiens hypothetical protein	1066	99
649	7492	AE003652	Drosophila melanogaster CG13284 gene product	587	40
650	7494	AE003526	Drosophila melanogaster CG4098 gene product	753	51
651	7498	AB033045	Homo sapiens KIAA1219 protein	2674	99
652	7504	X61381	Rattus rattus interferon-induced protein	202	46
653	7508	D38169	Homo sapiens inositol 1,4,5-trisphosphate 3-kinase isoenzyme	3278	100
654	7516	AL031432	Homo sapiens dJ465N24.2.1 (PUTATIVE novel protein) (isoform 1)	893	100
655	7518	U79275	Homo sapiens unknown	611	100
656	7519	AJ011306	Homo sapiens guanine nucleotide exchange	2752	99

TABLE 2

			factor (long isoform)		
657	7521	AL355775	Arabidopsis thaliana putative protein	368	48
658	7529	AF116827	Homo sapiens unknown	3020	99
659	7532	AE003795	Drosophila melanogaster CG15120 gene product	630	59
660	7533	AB031292	Mus musculus proteolipid protein 2	130	31
661	7535	U25801	Homo sapiens Tax1 binding protein	852	98
662	7545	AF049523	Homo sapiens huntingtin-interacting protein HYPA/FBP11	1390	97
663	7546	AK001809	Homo sapiens unnamed protein product	1040	100
664	7552	AF028823	Homo sapiens Tax interaction protein 1	581	100
665	7554	AE003467	Drosophila melanogaster CG13880 gene product	262	41
666	7567	U94991	Xenopus laevis transcription factor XLMO1	795	97
667	7569	S73775	Homo sapiens calmitine; calsequestrine	2029	100
668	7575	AE003579	Drosophila melanogaster CG17593 gene product	1023	45
669	7576	AJ243191	Homo sapiens heat shock protein	827	96
670	7577	X65020	Bos taurus PSST subunit of the NADH: ubiquinone oxidoreductase complex	964	86
671	7579	AE003731	Drosophila melanogaster CG10877 gene product	495	49
672	7582	Z30093	Homo sapiens basic transcription factor 2, 35 kD subunit	1576	99
673	7587	AB030835	Homo sapiens contains two glutamine rich domains, three zinc-finger domains, and matrin 3 homologous domain 3 (MH3)	4697	99
674	7589	AB023222	Homo sapiens KIAA1005 protein	5410	100
675	7597	AL022238	Homo sapiens dJ1042K10.2 (supported by GENSCAN, FGENES and GENEWISE)	4048	99
676	7597	AL022238	Homo sapiens dJ1042K10.2 (supported	2321	99

TABLE 2

			by GENSCAN, FGENES and GENEWISE)		
677	7609	AL117237	Homo sapiens hypothetical protein	4820	99
678	7609	AK000726	Homo sapiens unnamed protein product	3767	96
679	7609	AK000726	Homo sapiens unnamed protein product	3227	92
680	7613	AL023859	Schizosaccharomyces pombe trna-splicing endonuclease subunit	172	42
681	7623	AC005023	Homo sapiens match to EST AA361117 (NID:g2013436)	789	100
682	7629	AC005253	Homo sapiens R26445_1	902	100
683	7630	AF151070	Homo sapiens HSPC236	951	98
684	7633	AF103801	Homo sapiens unknown	2555	100
685	7635	AC004000	Homo sapiens match to EST AA085966 (NID:g1629547)	388	100
686	7638	AK001712	Homo sapiens unnamed protein product	1586	99
687	7639	M24103	Bos taurus translocase	1512	97
688	7646	D79990	Homo sapiens KIAA0168	899	60
689	7647	AF208844	Homo sapiens BM-002	428	100
690	7648	AL023496	Streptomyces coelicolor A3(2) hypothetical protein	163	35
691	7658	AL031431	Homo sapiens dJ462O23.2 (novel protein)	2058	100
692	7664	S45367	Canis familiaris centractin	1949	100
693	7664	S45367	Canis familiaris centractin	1315	98
694	7672	U88573	Homo sapiens NBR2	566	92
695	7674	D43950	Homo sapiens KIAA0098 protein	2732	100
696	7675	AE003708	Drosophila melanogaster CG5038 gene product	930	40
697	7676	AL080125	Homo sapiens hypothetical protein	3002	100
698	7681	AE003690	Drosophila melanogaster CG14701 gene product	276	67
699	7688	AL080125	Homo sapiens hypothetical protein	3181	100
700	7693	Z14000	Homo sapiens RING1	2017	100
701	7694	AC013289	Arabidopsis thaliana hypothetical protein	189	44
702	7715	AB041607	Mus musculus unnamed protein product	2345	94
703	7716	AF251041	Homo sapiens SGC32445 protein	535	70

TABLE 2

704	7718	AE003427	Drosophila melanogaster CG10802 gene product	527	51
705	7721	AC012329	Arabidopsis thaliana putative transporter	690	38
706	7723	X67250	Rattus norvegicus n-chimaerin	1710	97
707	7729	U05784	Rattus norvegicus light chain 3 subunit of microtubule-associated proteins 1A and 1B	609	96
708	7733	S77099	Drosophila pseudoobscura Jan A	276	48
709	7735	AF060862	Homo sapiens unknown	638	96
710	7741	AL133363	Arabidopsis thaliana putative protein	155	38
711	7743	AB034912	Homo sapiens WD-repeat like sequence	2483	100
712	7748	AF177145	Homo sapiens mammalian inositol hexakisphosphate kinase 2	2232	99
713	7749	X69910	Homo sapiens P63 protein	2958	99
714	7750	U80736	Homo sapiens CAGF9	1657	100
715	7757	AC004997	Homo sapiens match to ESTs AA667999 (NID:g2626700), AA165465 (NID:g1741481), Z45871 (NID:g575105), and T84026 (NID:g712314); similar to various tre-like proteins including: AF040654 (PID:g2746883), D13644 (PID:g2104571), AL0211483 (PID:g2815076), and Z797052 (PID:g2213552)	2335	100
716	7759	AK000504	Homo sapiens unnamed protein product	1045	100
717	7760	AE003565	Drosophila melanogaster CG12756 gene product	345	48
718	7760	AE003565	Drosophila melanogaster CG12756 gene product	345	48
719	7764	AF193795	Homo sapiens vacuolar sorting protein VPS29/PEP11	960	100
720	7765	AJ222968	Mus musculus L-periaxin	120	30
721	7766	AK001456	Homo sapiens unnamed protein product	4311	100

TABLE 2

722	7767	AE003431	Drosophila melanogaster CG15912 gene product	322	36
723	7769	AK000505	Homo sapiens unnamed protein product	2190	100
724	7770	AE003525	Drosophila melanogaster CG7725 gene product	383	42
725	7774	U37251	Homo sapiens Description: KRAB zinc finger protein; this is a splicing variant that contains a stop codon and frame shift between the KRAB box and the zinc finger region; Method: conceptual translation supplied by author	196	44
726	7779	AF233321	Mus musculus zinc transporter like 1	1864	94
727	7781	AE003790	Drosophila melanogaster CG3450 gene product	339	86
728	7782	X95826	Homo sapiens mono-ADP-ribosyltransferase	1390	98
729	7783	M12098	Rattus norvegicus myosin heavy chain	155	25
730	7787	AF140683	Mus musculus F-box protein FWD2	2397	98
731	7792	AF151023	Homo sapiens HSPC189	1104	100
732	7795	AL117639	Homo sapiens hypothetical protein	1342	99
733	7801	AB007829	Homo sapiens CSR1	528	54
734	7807	AJ243972	Homo sapiens 6-phosphogluconolactonase	1317	100
735	7808	AB035863	Homo sapiens ATP specific succinyl CoA synthetase beta subunit precursor	2324	99
736	7819	AB015339	Homo sapiens HRIHFB2255	575	66
737	7824	AF163825	Homo sapiens pre-B lymphocyte protein 3	634	100
738	7826	AF201949	Homo sapiens 60S ribosomal protein L30 isolog	868	100
739	7829	AF060862	Homo sapiens unknown	236	85
740	7832	AJ011373	Homo sapiens hypothetical protein	549	100
741	7839	AL031778	Homo sapiens dJ34B21.3 (PUTATIVE novel protein)	421	100
742	7844	AK000452	Homo sapiens unnamed protein product	1473	100

TABLE 2

743	7847	AK001851	Homo sapiens unnamed protein product	2711	99
744	7848	AK000510	Homo sapiens unnamed protein product	1536	100
745	7853	U89649	Chlamydomonas reinhardtii Mr19,000 outer arm dynein light chain	244	34
746	7854	AL050008	Homo sapiens hypothetical protein	591	56
747	7856	AJ009985	Homo sapiens annexin 31 (annexin XXXI)	1675	99
748	7862	AL080097	Homo sapiens hypothetical protein	1363	100
749	7865	AF224263	Heterodontus francisci HoxD8	742	84
750	7874	X63417	Homo sapiens IRLB	1037	100
751	7877	AE003485	Drosophila melanogaster CG11757 gene product	622	53
752	7880	AK001939	Homo sapiens unnamed protein product	2532	99
753	7882	AF263614	Homo sapiens acetyl-CoA synthetase	3493	99
754	7884	AF022977	Caenorhabditis elegans contains similarity to leucine-rich repeats (LRR)	177	36
755	7886	AC006153	Homo sapiens similar to Aquifex aeolicus GTP-binding protein; similar to AE000771 (PID:g2984292)	662	98
756	7888	AE003734	Drosophila melanogaster CG3337 gene product	416	47
757	7889	AF110764	Mus musculus RS21-C6	655	75
758	7901	AE003459	Drosophila melanogaster CG9848 gene product	507	59
759	7910	AF177476	Rattus norvegicus CDK5 activator-binding protein	1995	86
760	7911	AL049946	Homo sapiens hypothetical protein	3091	99
761	7921	AL121733	Homo sapiens hypothetical protein	314	39
762	7923	AE003772	Drosophila melanogaster CG15525 gene product	299	46
763	7924	AE003834	Drosophila melanogaster BcDNA:GH08789 gene product	710	42
764	7925	U16307	Homo sapiens glioma pathogenesis-related	329	40

TABLE 2

			protein		
765	7928	AF161457	Homo sapiens HSPC339	571	100
766	7929	AL050137	Homo sapiens hypothetical protein	2319	100
767	7930	AF223466	Homo sapiens HT015 protein	831	66
768	7934	AL132965	Arabidopsis thaliana putative WD-40 repeat-protein	286	30
769	7938	AB024937	Homo sapiens LUNX	1284	100
770	7942	Y14768	Homo sapiens V-ATPase G-subunit like protein	579	100
771	7945	AL110235	Homo sapiens hypothetical protein	870	100
772	7946	L13291	Homo sapiens ADP-ribosylarginine hydrolase	802	46
773	7948	AK000771	Homo sapiens unnamed protein product	1067	99
774	7951	AE003808	Drosophila melanogaster CG8441 gene product	319	54
775	7952	X92814	Homo sapiens homologous to rat HREV107 (ACC.NO. X76453)	830	99
776	7953	AF151638	Homo sapiens phosphatidylcholine transfer protein	1142	100
777	7954	AF059531	Homo sapiens protein arginine N-methyltransferase 3	2679	99
778	7957	AF161392	Homo sapiens HSPC274	370	79
779	7958	AL050100	Homo sapiens hypothetical protein	165	53
780	7961	AL117444	Homo sapiens hypothetical protein	1991	100
781	7965	X83006	Homo sapiens neutrophil gelatinase associated lipocalin	208	40
782	7966	U34973	Mus musculus protein tyrosine phosphatase-like	1131	95
783	7979	M86510	Schistosoma mansoni glutathione peroxidase	327	43
784	7986	AE000850	Methanobacterium thermoautotrophicum transcriptional regulator	407	55
785	7986	AE000850	Methanobacterium thermoautotrophicum transcriptional regulator	406	55
786	7988	AF161455	Homo sapiens HSPC337	742	98
787	7991	Z48795	Caenorhabditis elegans similarity to a	247	38

TABLE 2

			thioredoxin-like protein from Bacillus subtilis (Swiss Prot accession number P35160)~cDNA EST EMBL:D69151 comes from this gene~cDNA EST EMBL:D69212 comes from this gene~cDNA EST EMBL:D76199 comes from this gene~cDNA EST EMBL:D76335 comes from this gene~cDNA EST EMBL:D65648 comes from this gene~cDNA EST EMBL:D65690 comes from this gene~cDNA EST EMBL:D73198 comes from this gene~cDNA EST EMBL:D73307 comes from this gene~cDNA EST yk257e10.3 comes from this gene~cDNA EST yk257e10.5 comes from this gene~cDNA EST yk228e3.3 comes from this gene~cDNA EST yk228e3.5 comes from this gene~cDNA EST yk199h7.5 comes from this gene		
788	7992	AJ005866	Homo sapiens Sqv-7-like protein	1321	99
789	7992	AJ005866	Homo sapiens Sqv-7-like protein	1118	99
790	7992	AJ005866	Homo sapiens Sqv-7-like protein	891	99
791	7992	AJ005866	Homo sapiens Sqv-7-like protein	1016	99
792	8003	AB040964	Homo sapiens KIAA1531 protein	337	31
793	8014	AL117587	Homo sapiens hypothetical protein	902	100
794	8015	AL031010	Homo sapiens dJ422F24.1 (PUTATIVE novel protein similar to C. elegans C02C2.5)	968	100
795	8016	U28016	Mus musculus parathion hydrolase (phosphotriesterase)-related protein	1624	87
796	8017	AK001704	Homo sapiens unnamed protein product	2207	99
797	8019	AF117587	Manduca sexta unknown	348	71
798	8020	AB018260	Homo sapiens KIAA0717 protein	3331	99

TABLE 2

799	8022	AE003446	Drosophila melanogaster CG12121 gene product	772	51
800	8022	AE003446	Drosophila melanogaster CG12121 gene product	1074	52
801	8028	AL137520	Homo sapiens hypothetical protein	2032	99
802	8030	AF182076	Homo sapiens glioma tumor suppressor candidate region protein 2	2418	100
803	8038	AE003552	Drosophila melanogaster CG3967 gene product	388	43
804	8042	AL159143	Homo sapiens hypothetical protein	1045	60
805	8045	L40357	Homo sapiens thyroid receptor interactor	509	100
806	8045	L40357	Homo sapiens thyroid receptor interactor	404	85
807	8046	Y18503	Homo sapiens XAP-5-like protein	1672	100
808	8047	AB041600	Mus musculus unnamed protein product	1053	87
809	8051	AL049688	Homo sapiens hypothetical protein	2514	98
810	8059	AK001355	Homo sapiens unnamed protein product	625	41
811	8064	Z14122	Xenopus laevis XLCL2	455	77
812	8069	X67712	Psychrobacter immobilis triacylglycerol lipase	272	28
813	8074	AB033105	Homo sapiens KIAA1279 protein	3221	99
814	8077	AK001963	Homo sapiens unnamed protein product	952	100
815	8078	AJ000217	Homo sapiens CLIC2	1286	99
816	8079	AB030505	Mus musculus UBE-1c2	1069	79
817	8084	AL080118	Homo sapiens hypothetical protein	738	96
818	8088	AE003829	Drosophila melanogaster CG11777 gene product	641	71
819	8090	AL023553	Homo sapiens dJ347H13.4 (novel protein)	557	100
820	8091	AL109978	Homo sapiens hypothetical protein	1679	100
821	8099	AE003839	Drosophila melanogaster CG8722 gene product	1037	58
822	8099	AE003839	Drosophila melanogaster CG8722 gene product	678	53
823	8100	AF180681	Homo sapiens guanine	3597	100

TABLE 2

			nucleotide exchange factor		
824	8102	AK001433	Homo sapiens unnamed protein product	944	100
825	8103	M62419	Mus musculus clathrin-associated protein	2189	99
826	8103	AJ006219	Drosophila melanogaster clathrin-associated protein	1254	79
827	8104	AB006191	Mus musculus cornichon-like protein	362	78
828	8108	L03303	Oryctolagus cuniculus small GTP-binding protein	1034	96
829	8110	AB037823	Homo sapiens KIAA1402 protein	4037	100
830	8116	A84493	unidentified unnamed protein product	3309	100
831	8117	AB030184	Mus musculus contains transmembrane (TM) region and ATP binding region	1586	92
832	8123	AL023694	Homo sapiens dJ511E16.2 (putative protein based on ESTs)	663	100
833	8130	AK001138	Homo sapiens unnamed protein product	2182	99
834	8130	AK001138	Homo sapiens unnamed protein product	1858	99
835	8143	AL022157	Homo sapiens SPIN (SPINDLIN HOMOLOG (PROTEIN DXF34))	1233	100
836	8143	AL022157	Homo sapiens SPIN (SPINDLIN HOMOLOG (PROTEIN DXF34))	1233	100
837	8154	AK001914	Homo sapiens unnamed protein product	2176	99
838	8155	AL020996	Homo sapiens dJ317E23.2 (novel protein with remote similarity to KIAA0009)	1492	100
839	8162	Z69637	Caenorhabditis elegans predicted using Genefinder~Similarity to E.coli hypothetical protein YCAC (SW:YCAC_ECOLI)~cDNA EST yk555d12.3 comes from this gene	240	57
840	8163	AB023167	Homo sapiens KIAA0950 protein	1664	100
841	8172	AE003527	Drosophila melanogaster CG4729 gene product	737	40
842	8173	AK001350	Homo sapiens unnamed	1730	99

TABLE 2

			protein product		
843	8179	AF131852	Homo sapiens Unknown	473	100
844	8182	AF186593	Homo sapiens butyrophilin-like	406	27
845	8183	AC008015	Homo sapiens unknown	815	96
846	8184	AE003499	Drosophila melanogaster CG7860 gene product	558	42
847	8185	AK001441	Homo sapiens unnamed protein product	378	46
848	8187	AJ272267	Homo sapiens choline dehydrogenase	2449	100
849	8188	AB001773	Ciona savignyi PEM-6	196	34
850	8190	AC004955	Homo sapiens supported by ESTs T61992 (NID:g665235) and W26450 (NID:g1307167) and Genscan	1618	85
851	8190	AC004955	Homo sapiens supported by ESTs T61992 (NID:g665235) and W26450 (NID:g1307167) and Genscan	1618	85
852	8192	AF113534	Homo sapiens HP1-BP74 protein	2723	96
853	8193	AF232226	Danio rerio Dedd1	191	42
854	8197	AF132732	Homo sapiens unknown	1116	70
855	8197	AF132732	Homo sapiens unknown	1010	74
856	8199	AB040905	Homo sapiens KIAA1472 protein	3062	99
857	8202	AB018268	Homo sapiens KIAA0725 protein	3013	100
858	8203	AE003800	Drosophila melanogaster CG5742 gene product	648	53
859	8208	AL117442	Homo sapiens hypothetical protein	1344	100
860	8209	AF040964	Homo sapiens unknown protein IT1	3033	100
861	8211	AB020713	Homo sapiens KIAA0906 protein	4668	99
862	8214	AJ245417	Homo sapiens G5b protein	794	100
863	8217	AB037859	Homo sapiens KIAA1438 protein	4761	99
864	8223	AE003469	Drosophila melanogaster CG13886 gene product	352	45
865	8224	X58769	Homo sapiens V alpha gene segment	284	83
866	8226	AC012680	Arabidopsis thaliana putative protein phosphatase 2C	209	38
867	8227	AF132174	Drosophila melanogaster unknown	563	54

TABLE 2

868	8229	AK000576	Homo sapiens unnamed protein product	1342	100
869	8232	AE003638	Drosophila melanogaster CG5142 gene product	1420	47
870	8236	Y11710	Homo sapiens collagen type XIV	1048	97
871	8239	X82240	Homo sapiens T cell leukemia/lymphoma 1	617	100
872	8244	U42841	Caenorhabditis elegans short region of weak similarity to collagen	161	34
873	8245	AF023130	Homo sapiens Ras-GRF2	6413	100
874	8248	AJ131613	Homo sapiens dicarboxylate carrier protein	1470	99
875	8251	L27645	Danio rerio growth-associated protein	130	37
876	8253	AF141377	Mus musculus Ly-6/neurotoxin homolog	527	81
877	8260	AF217544	Xenopus laevis ornithine decarboxylase-2	1451	59
878	8262	AF136631	Homo sapiens neuritin	182	33
879	8268	X67098	Homo sapiens ORF1	493	100
880	8270	AB033064	Homo sapiens KIAA1238 protein	1480	100
881	8272	AF154831	Rattus norvegicus PV-1	1403	60
882	8274	AF026528	Rattus norvegicus stathmin-like-protein RB3	915	99
883	8274	AF026530	Rattus norvegicus stathmin-like-protein splice variant RB3''	1093	97
884	8275	U35244	Rattus norvegicus vacuolar protein sorting homolog r-vps33a	2981	96
885	8277	AL353814	Arabidopsis thaliana putative protein	425	30
886	8281	AF157318	Homo sapiens AD-017 protein	912	47
887	8283	AK000461	Homo sapiens unnamed protein product	1594	100
888	8289	AE003681	Drosophila melanogaster CG11986 gene product	518	38
889	8295	AL031775	Homo sapiens dJ30M3.3 (novel protein similar to C. elegans Y63D3A.4)	1902	100
890	8300	M21103	Ovis aries BIIIB4 high-sulfur keratin	484	82
891	8303	Z85986	Homo sapiens dJ108K11.3 (similar to yeast suppressor	1143	75

TABLE 2

			protein SRP40)		
892	8304	U18762	Rattus norvegicus retinol dehydrogenase type I	890	52
893	8305	AF072467	Homo sapiens unknown	2495	100
894	8309	AB037779	Homo sapiens KIAA1358 protein	2271	100
895	8318	AE003491	Drosophila melanogaster CG2453 gene product	527	59
896	8319	AF136631	Homo sapiens neuritin	742	100
897	8321	AF207989	Homo sapiens orphan G-protein coupled receptor	2326	100
898	8322	Z97630	Homo sapiens dJ466N1.4 (novel protein similar to ANK3 (ankyrin 3, node of Ranvier (ankyrin G)))	181	44
899	8323	U21549	Mus musculus Ac39/physophilin	1280	68
900	8325	AF036694	Caenorhabditis elegans CD4.4 gene product	189	25
901	8331	AF117814	Mus musculus odd-skipped related 1 protein	945	68
902	8332	AE003442	Drosophila melanogaster CG2256 gene product	360	50
903	8333	AK002084	Homo sapiens unnamed protein product	2469	100
904	8335	AL008729	Homo sapiens predicted protein dJ257A7.2	737	100
905	8336	AB032986	Homo sapiens KIAA1160 protein	1458	100
906	8337	AK000523	Homo sapiens unnamed protein product	1563	99
907	8340	AE003658	Drosophila melanogaster CG7200 gene product	436	47
908	8343	AK001344	Homo sapiens unnamed protein product	1436	99
909	8347	AK002182	Homo sapiens unnamed protein product	1810	99
910	8349	AK001715	Homo sapiens unnamed protein product	715	99
911	8351	AF155100	Homo sapiens zinc finger protein NY-REN-21 antigen	2261	100
912	8353	J05071	Bos taurus GTP-binding regulatory protein gamma-6 subunit	356	100
913	8355	AK001046	Homo sapiens unnamed protein product	1173	99
914	8361	AL050170	Homo sapiens hypothetical protein	714	100

TABLE 2

915	8365	X64002	Homo sapiens RAP74	2661	99
916	8367	X04085	Homo sapiens catalase	2846	100
917	8369	AJ278124	Homo sapiens hypothetical protein	1570	100
918	8370	Z48745	Mus musculus ABC8	1101	69
919	8375	AF045564	Rattus norvegicus development-related protein	1715	93
920	8387	X97571	Mus musculus HCMV-interacting protein	479	96
921	8391	L08239	Homo sapiens located at OATL1	2274	100
922	8393	AF121863	Homo sapiens sorting nexin 14	1964	100
923	8393	AF121863	Homo sapiens sorting nexin 14	1203	84
924	8394	AL050101	Homo sapiens hypothetical protein	2848	100
925	8395	AE003681	Drosophila melanogaster CG11990 gene product	1517	59
926	8396	Y18101	Mus musculus macrophage actin-associated-tyrosine-phosphorylated protein	1559	87
927	8398	AL050318	Homo sapiens dJ977B1.4 (novel protein similar to TGIF (TG-interacting factor (TALE family homeobox)))	1224	100
928	8402	AB026264	Homo sapiens IMPACT	1694	100
929	8402	AB026264	Homo sapiens IMPACT	1123	100
930	8405	Z82062	Caenorhabditis elegans cDNA EST yk415c12.5 comes from this gene~cDNA EST yk526h3.3 comes from this gene~cDNA EST yk599b1.3 comes from this gene	431	42
931	8406	AK001692	Homo sapiens unnamed protein product	2492	99
932	8409	AL035602	Arabidopsis thaliana putative protein	499	28
933	8410	AL050107	Homo sapiens hypothetical protein	1342	100
934	8414	AK000508	Homo sapiens unnamed protein product	503	100
935	8415	AL021453	Homo sapiens dJ821D11.3 (PUTATIVE protein)	856	100
936	8419	AJ276003	Homo sapiens GAR1 protein	1216	100
937	8426	D26185	Bacillus subtilis unknown	365	33

TABLE 2

938	8430	AC004874	Homo sapiens similar to N-acetylgalactosaminyltransferase; similar to Q07537 (PID:g1171989)	957	100
939	8431	AF199597	Homo sapiens A-type potassium channel modulatory protein 1	1139	100
940	8432	Y13148	Rattus norvegicus PAG608	1350	88
941	8433	M24852	Rattus norvegicus neuron-specific protein PEP-19	124	46
942	8434	AF146738	Rattus norvegicus testis specific protein	771	83
943	8438	AK000427	Homo sapiens unnamed protein product	358	36
944	8439	AB017644	Homo sapiens ubiquitin-conjugating enzyme E2	919	85
945	8441	AC006538	Homo sapiens BC41195_1	831	78
946	8450	AB004316	Bos taurus mitochondrial methionyl-tRNA transformylase	1556	88
947	8451	Z35094	Homo.sapiens SURF-2	1354	97
948	8452	AL050275	Homo sapiens hypothetical protein	2351	99
949	8460	AC006014	Homo sapiens similar to RFP transforming protein; similar to P14373 (PID:g132517)	1299	100
950	8461	AC005099	Homo sapiens match to AI222572 (NID:g3804775)	469	100
951	8462	V00507	Homo sapiens coding sequence of DHFR (1 is 1st base in codon) (561 is 3rd base in codon)	984	100
952	8464	AL049709	Homo sapiens dJ18C9.2 (novel gene (locus D20S101) similar to Gamma-glutamyltranspeptidase, contains CCA trinucleotide repeat, based on Genscan and Fgenesh predictions.)	3370	99
953	8465	AF173871	Mus musculus neuronal PAS3	977	94
954	8467	AF178983	Homo sapiens Ras-associated protein Rap1	433	97
955	8470	AB037858	Homo sapiens KIAA1437	1724	58

TABLE 2

			protein		
956	8471	AF109674	Rattus norvegicus late gestation lung protein 1	846	74
957	8473	AF061346	Mus musculus Edp1 protein	1077	64
958	8474	AK000343	Homo sapiens unnamed protein product	1272	100
959	8475	AF233582	Mus musculus GTPase Rab37	942	95
960	8476	AF195951	Homo sapiens signal recognition particle 68	3127	98
961	8480	AL080168	Homo sapiens hypothetical protein	2128	100
962	8482	AE003713	Drosophila melanogaster CG14898 gene product	207	44
963	8482	AE003713	Drosophila melanogaster CG14898 gene product	91	60
964	8486	Z81592	Caenorhabditis elegans predicted using Genefinder	426	55
965	8488	AK000559	Homo sapiens unnamed protein product	1319	99
966	8492	Z71181	Caenorhabditis elegans similar to hydrolase	601	38
967	8494	Z81105	Caenorhabditis elegans similar to alpha/beta hydrolase fold-cDNA EST EMBL:T02320 comes from this gene	460	40
968	8496	S94421	Homo sapiens T cell receptor eta-exon	478	100
969	8497	AL050214	Homo sapiens hypothetical protein	949	99
970	8499	AF161380	Homo sapiens HSPC262	772	100
971	8513	AE003802	Drosophila melanogaster CG14480 gene product	423	44
972	8522	AK001972	Homo sapiens unnamed protein product	520	38
973	8526	U41012	Caenorhabditis elegans C06A6.3 gene product	172	24
974	8531	AE003635	Drosophila melanogaster CG5336 gene product	1064	50
975	8533	AJ001019	Homo sapiens ring finger protein	1301	100
976	8542	AF003388	Caenorhabditis elegans R10F2.5 gene product	346	37
977	8544	AF178632	Homo sapiens FEM-1-like death receptor binding protein	3261	100
978	8565	AC006033	Homo sapiens similar	1195	100

TABLE 2

			to MLN 64; similar to I38027 (PID:g2135214)		
979	8565	AC006033	Homo sapiens similar to MLN 64; similar to I38027 (PID:g2135214)	668	93
980	8572	AB023811	Homo sapiens TU3A	351	55
981	8576	AE003802	Drosophila melanogaster CG4996 gene product	362	37
982	8578	AF065441	Mus musculus FGF binding protein 1	174	24
983	8584	AK000367	Homo sapiens unnamed protein product	3440	98
984	8598	D87463	Homo sapiens KIAA0273	1396	76
985	8602	AL117600	Homo sapiens hypothetical protein	2786	99
986	8604	AJ249735	Homo sapiens claudin-6	1142	100
987	8609	X57560	Escherichia coli pspE protein	535	100
988	8612	AF169284	Homo sapiens LIM and cysteine-rich domains protein 1	1997	100
989	8637	AE003559	Drosophila melanogaster CG8576 gene product	592	46
990	8640	AB024523	Homo sapiens basic kruppel like factor	1206	100
991	8643	X55989	Homo sapiens eosinophil cationic-related protein	737	99
992	8645	AF007151	Homo sapiens unknown	1481	100
993	8650	X52904	Escherichia coli open reading frame (AA 1-65)	359	100
994	8651	U19577	Escherichia coli galactonate dehydratase	242	93
995	8654	AL117660	Homo sapiens hypothetical protein	447	100
996	8655	AK001355	Homo sapiens unnamed protein product	1553	100
997	8657	AE003693	Drosophila melanogaster CG18347 gene product	686	54
998	8665	AF044774	Homo sapiens breakpoint cluster region protein 2	2681	99
999	8668	AL008729	Homo sapiens predicted protein dJ257A7.1	416	100
1000	8671	X82693	Homo sapiens E48 antigen	620	96
1001	8672	AE003499	Drosophila melanogaster CG7872 gene product	692	51
1002	8692	AF131218	Homo sapiens chromosome 16 open	1493	100

TABLE 2

			reading frame 5		
1003	8706	AL021396	Homo sapiens dJ971N18.2	1375	100
1004	8716	AF196972	Homo sapiens JM24 protein	2239	100
1005	8719	AF053356	Homo sapiens insulin receptor substrate like protein	228	97
1006	8743	AL050214	Homo sapiens hypothetical protein	949	99
1007	8764	AF153127	Gallus gallus SAPK interacting protein	2442	89
1008	8764	AF153127	Gallus gallus SAPK interacting protein	1477	83
1009	8764	AF153127	Gallus gallus SAPK interacting protein	1651	86
1010	8774	X56932	Homo sapiens 23 kD highly basic protein	1044	100
1011	8782	AF174605	Homo sapiens F-box protein Fbx25	467	70
1012	8796	AB033097	Homo sapiens KIAA1271 protein	2824	100
1013	8827	Y17013	porcine endogenous retrovirus pol	304	64
1014	8842	AE003416	Unknown symbol=BG:DS01068.6; cDNA=method:''sim4'', score:''1000.0'', desc:''LD09509 LD Drosophila	1550	48
1015	8842	AE003416	Unknown symbol=BG:DS01068.6; cDNA=method:''sim4'', score:''1000.0'', desc:''LD09509 LD Drosophila	1207	45
1016	8858	AL133215	Homo sapiens bA108L7.2 (novel protein similar to rat tricarboxylate carrier)	1322	99
1017	8871	AK001721	Homo sapiens unnamed protein product	1707	99
1018	8921	U29495	Mus musculus Zfp61p	299	52
1019	8927	AK001344	Homo sapiens unnamed protein product	1086	100
1020	8942	AF146568	Homo sapiens MIL1 protein	1936	100
1021	8994	AE003802	Drosophila melanogaster CG6410 gene product	349	42
1022	9023	U10362	Homo sapiens GP36b glycoprotein	1001	55
1023	9028	AB018341	Homo sapiens KIAA0798 protein	307	70
1024	9058	AE003442	Drosophila melanogaster CG10778	636	54

TABLE 2

			gene product		
1025	9058	AE003442	Drosophila melanogaster CG10778 gene product	429	53
1026	9079	AB027004	Homo sapiens protein phosphatase	1018	100
1027	9079	AB027003	Mus musculus protein phosphatase	378	84
1028	9082	U64856	Caenorhabditis elegans weak similarity to TPR domains	215	40
1029	9084	AL110241	Homo sapiens hypothetical protein	1240	97
1030	9093	X76717	Homo sapiens MT-1l protein	204	89
1031	9101	AK001818	Homo sapiens unnamed protein product	910	100
1032	9103	AK001182	Homo sapiens unnamed protein product	1752	94
1033	9105	AF187016	Homo sapiens myosin regulatory light chain interacting protein MIR	2303	99
1034	9151	AB037730	Homo sapiens KIAA1309 protein	894	35
1035	9161	AK001659	Homo sapiens unnamed protein product	1886	99
1036	9172	Plasmodium falciparum	3' end., gene product	178	23
1037	9174	AK001324	Homo sapiens unnamed protein product	2657	99
1038	9204	AF161548	Homo sapiens HSPC063	1018	98
1039	9234	AB041581	Mus musculus unnamed protein product	1758	95
1040	9235	X98507	Homo sapiens myosin I beta	5288	99
1041	9239	AL133107	Homo sapiens hypothetical protein	1388	100
1042	9256	D90869	Escherichia coli similar to	2047	100
1043	9276	A12029	Homo sapiens MRP-14	613	100
1044	9345	AC005328	Homo sapiens R26660_1, partial CDS	870	74
1045	9379	AC024876	Caenorhabditis elegans contains similarity to SW:RPB1_CRIGR	829	61
1046	9435	AB014536	Homo sapiens KIAA0636 protein	1876	64
1047	9437	U85055	Mus musculus rap1/rap2 interacting protein	2103	90
1048	9469	AP000060	Aeropyrum pernix 264aa long hypothetical protein	108	33
1049	9500	AE003638	Drosophila	583	48

TABLE 2

			melanogaster CG12404 gene product		
1050	9502	X78927	Homo sapiens zinc finger protein	3865	99
1051	9520	AL163279	Homo sapiens homolog to cAMP response element binding and beta transducin family proteins	5035	99
1052	9541	Z48475	Homo sapiens glucokinase regulator	3160	99
1053	9541	Z48475	Homo sapiens glucokinase regulator	2682	97
1054	9548	AF195764	Homo sapiens megakaryocyte-enhanced gene transcript 1 protein; MEGT1 protein	2055	99
1055	9556	AC004382	Homo sapiens Unknown gene product	1593	100
1056	9556	AC004382	Homo sapiens Unknown gene product	984	100
1057	9575	AL117352	Homo sapiens dJ876B10.3 (novel protein similar to C. elegans T19B10.6 (Tr:Q22557))	2581	99
1058	9589	AE003454	Drosophila melanogaster CG10440 gene product	218	43
1059	9599	AJ245621	Homo sapiens CTL2 protein	3728	99
1060	9602	AE003673	Drosophila melanogaster CG1939 gene product	440	40
1061	9606	X05562	Homo sapiens alpha-2 chain precursor (AA -25 to 1018) (3416 is 2nd base in codon)	5908	99
1062	9622	Z98048	Homo sapiens dJ408N23.4 (novel DnaJ domain protein)	1296	99
1063	9623	AF154415	Homo sapiens FLASH	10253	100
1064	9646	U20286	Rattus norvegicus lamina associated polypeptide 1C	1567	70
1065	9747	AB033101	Homo sapiens KIAA1275 protein	5625	99
1066	9773	AL117337	Homo sapiens bA393J16.1 (zinc finger protein 33a (KOX 31))	250	60
1067	9785	AC005328	Homo sapiens R26660_1, partial CDS	1126	100
1068	9801	AB033092	Homo sapiens KIAA1266 protein	3067	99
1069	9811	AE003633	Drosophila	961	76

TABLE 2

			melanogaster CG14939 gene product		
1070	9843	AL080080	Homo sapiens hypothetical protein	1508	100
1071	9854	AB037360	Homo sapiens ANKHZN	5734	95
1072	9854	AB037360	Homo sapiens ANKHZN	959	97
1073	9864	AF237676	Mus musculus G beta-like protein GBL	1721	96
1074	9864	AF237676	Mus musculus G beta-like protein GBL	1043	70
1075	9871	U26358	Rattus norvegicus S100A1 gene product	137	36
1076	9879	AF212162	Homo sapiens ninein	10369	99
1077	9881	AK000463	Homo sapiens unnamed protein product	1252	99
1078	9885	AC004890	Homo sapiens similar to zinc finger proteins; similar to BAA24380	542	86
1079	9901	AF187989	Homo sapiens zinc finger protein ZNF223	2665	99
1080	9912	AC035150	Homo sapiens Zinc finger protein ZNF221	3459	100
1081	9916	Z82095	Caenorhabditis elegans similar to PDZ domain (Also known as DHR or GLGF).~cDNA EST EMBL:M75803 comes from this gene	702	54
1082	9921	AF117610	Mus musculus inner centromere protein INCENP	583	58
1083	9925	X90840	Homo sapiens axonal transporter of synaptic vesicles	4584	99
1084	9930	AF148848	Homo sapiens myoneurin	3208	99
1085	9949	AB033037	Homo sapiens KIAA1211 protein	3939	98
1086	9951	AK001605	Homo sapiens unnamed protein product	647	96
1087	9959	AF140342	Homo sapiens autoantigen SS-N	37	36
1088	9973	AK001753	Homo sapiens unnamed protein product	193	82
1089	9982	AL133396	Homo sapiens dJ1068H6.4 (prion protein like protein doppel)	962	100
1090	9994	AK001192	Homo sapiens unnamed protein product	2550	100
1091	10021	AK001842	Homo sapiens unnamed protein product	546	100
1092	10041	Z54096	Schizosaccharomyces pombe hypothetical coiled-coil protein	320	40
1093	10045	AK001122	Homo sapiens unnamed	227	43

TABLE 2

			protein product		
1094	10067	Y12090	Lycopersicon esculentum putative 3,4-dihydroxy-2-butanone kinase	1040	42
1095	10073	X81058	Mus musculus tex261	1010	99
1096	10112	AB012084	Mus musculus ITM	194	30
1097	10117	AB030251	Homo sapiens GTPase activating protein ID-GAP	3233	99
1098	10132	AJ010585	Rattus rattus PTB-like protein	2684	99
1099	10169	X75760	Drosophila melanogaster LRR47	364	30
1100	10217	U76618	Mus musculus N-RAP	804	48
1101	10226	AC005578	Homo sapiens F20887_1, partial CDS	835	65
1102	10232	D90832	Escherichia coli ORF_ID:o341#12; similar to	360	100
1103	10237	X01563	Escherichia coli L5 (rp1E) (aa 1-179)	911	100
1104	10279	AL133206	Homo sapiens hypothetical protein	1820	99